Veterinary Toxicology

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Introduction and Preface

Introduction and Preface

This publication has been developed from teaching materials and course notes used in teaching veterinary and graduate students at the University of Illinois. The Internet publication of this material is intended to provide a resource to educators in veterinary medicine and animal toxicology and their students. The material is offered with no guarantee as to accuracy or completeness. Much of the material has not been reviewed by the editor or authors in recent years, and certainly additional new and old information exists that is relevant to the topics discussed. This is a work in progress, and revision and updates of individual chapters are scheduled. The editors and authors would appreciate feedback from readers about the content and suggestions for including new, additional, or revised information for individual chapters or toxicants, along with appropriate references. Similarly new contributions by qualified authors are also welcome, provided the IVIS editorial board and the associate editors of the book approve them.

Guide

The toxicants reviewed in this book are organized primarily by the affected organ system and symptoms. The extent of the contents can best be viewed by reviewing the Abbreviated Table of Contents or the fully expanded Table of Contents which allows linking to individual toxicants listed within individual organ system chapters. Individual toxicants can also be located via the alphabetically arranged index of toxicants, or by using the search engine provided.

The annotated tables of toxicants are provided to allow for a quick review of groups of toxicants, along with abbreviated information about species incidence and severity and time course of sequelae following exposure. The relevant annotated tables can be accessed at the beginning of each chapter and at the heading for each toxicant. Each toxicant can also be accessed from the associated table.

Students and most other readers can best start with the introductory chapters, and by browsing the abbreviated and full tables of contents. Teachers can likewise determine if the material contains sufficient or relevant information about specific toxicants or groups of toxicants to warrant directing students to specific web pages and suggesting or assigning these by providing the URL addresses(s) for the page(s).

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A Work In Progress

The development of this book and associated IVIS database is a project of the International Veterinary Information Service (IVIS) in collaboration with **Dr. Val Beasley** and **Dr. Robert Poppenga**, both of whom are veterinary toxicologists. The goal of the project is to have a depository of basic information covering important aspects of the discipline of veterinary toxicology, especially those dealing with individual toxic chemicals and groups of such chemicals encountered in veterinary medicine, and to make the information available to the international veterinary community in a format amenable to the submission of updates, additions and revisions by guest authors, co-authors, and section editors when new information becomes available. Please address comments or the submission of new information to the respective authors or editors (see links to IVIS contributors) or to the IVIS Editorial Office.

Section I: Concepts in Toxicology

Introduction to Toxicology

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This chapter introduces the topic of veterinary toxicology by reviewing definitions, types and sources of toxicants, factors that influence toxicity, regulatory toxicology, risk assessment, dose-response relationships, kinetics, and other areas of study that lie within the general discipline. The reader is also directed to suggested reading and references that cover these topics [1-7].

1. Definitions of Toxicology, Poisons, Toxicants and Xenobiotics

- Ecosystem Health: involves comprehensive evaluations of the environment, including the interactions among abiotic and biotic elements from a range of stressors, and considers strategies to protect its resources for the long term. Especially focused on the *long range* health and utility of both natural and human-altered ecosystems. Considers people a part of the ecosystem and integrates input from many stakeholders and various experts to endeavor to bring about ecological health. This term implies sustained provision of ecological services (clean air, clean water, climate control, food production); and it is achieved in significant part through maintenance of high levels of biodiversity.
- Toxicology: Knowledge (or science) of poisons, including their *chemical properties, identification*, *biological effects*, and the *treatment* of conditions they cause.
- Poison: Any solid, liquid, or gas that, when introduced into or applied to the body, can interfere with the life processes of cells of the organism - by its own inherent chemical properties - without acting mechanically and regardless of temperature.
- Poison = Toxicant: The term poison is now used less often. Reason: Historical application of the term (malicious) vs. a compound used as a feed additive, agricultural, or other chemical - manufactured to fulfill a perceived human need.
- Xenobiotic: Any substance, harmful or not, that is foreign to the body.

2. Specialties within Toxicology

- Clinical and/or diagnostic veterinary toxicology involves specialized training and experience with the various chemical substances including natural and synthetic agents (elements and compounds) that commonly cause disease conditions or residues in animals under veterinary care. Work relates to diagnosis and management; and research to alleviate problems for the future.
- Basic toxicology involves research into the fundamental mechanisms involved in toxicant action.
- Safety testing of drugs or other chemicals (agriculture, industrial, household, etc.).
- Industrial toxicology relates to worker safety.
- Food toxicology relates to natural contaminants, food and feed additives, toxic effects and chemoprotective effects of compounds in foods and feeds.
- Environmental toxicology (research, risk assessment/management and/or regulatory practice). Historically this primarily involved concern for humans due to environmental exposures (may include the home, yard, air, water, golf course, farm, etc.). Also, this area of toxicology has most often considered anthropogenic (manmade) compounds.
- Ecotoxicology generally considers effects on organisms other than man (research and risk assessment/management). Challenge is to pick the "key species", and/or "species of interest". Usually involves animals, but should involve microbes, plants, and animals. Types and degrees of environmental exposures, environmental transport and fate, and altered species interactions as a result of toxicant exposure make this area of toxicology particularly challenging.

3. Categories of Toxicants often Encountered in Veterinary Practice

Veterinary practitioners and clinical veterinary toxicologists are most often concerned with the following toxicant groups:

- Pesticides (Includes insecticides, rodenticides, herbicides, avicides, etc according to the “pest” category to be controlled)

- Drugs (veterinary and human)
- Household chemicals
- Workplace chemicals
- Toxins
    - Bacterial
    - Fungal
    - Plant
    - Animal
- Feed additives
- Poisonous gases

4. Sources of Natural Toxicants and those Produced Outside of Living Organisms

1. **Naturally Occurring Toxicants**
    a. **Naturally occurring elements and compounds in the atmosphere, soil, and water**. e.g., carbon dioxide, nitrate, fluoride, copper, lead, selenium.
    b. **Toxins**
        - *Toxin* and *biotoxin* are synonyms. The term implies only a toxic compound which has been manufactured by a living organism.
        - *Bacterial toxins* (endotoxins, exotoxins).
        - *Mycotoxins* (in veterinary medicine, usually implies toxins from mycelial fungi); but in human medicine, the term mycotoxin is more often taken to mean a toxin from a mushroom.
        - *Plant toxins* also known as *phytotoxins*.
        - *Algal toxins* such as from blue-green algae as well as marine organisms such as dinoflagellates are collectively called*phycotoxins*. Blue-green algae are also termed cyanobacteria which are photosynthetic bacteria. Some of the phycotoxins of the marine dinoflagellates are known to bioaccumulate in food chains.
        - *Animal toxins* also known as zootoxins.
    c. Note: **Some poisonous gases are produced by bacteria** (e.g., ammonia, hydrogen sulfide).

2. **Produced outside of living organisms**
    a. Produced through chemical manufacturing.
    b. *Produced on purpose*: (e.g., synthetic drugs such as acetaminophen, or pesticides such as the now banned herbicide 2,4,5-T).
    c. *By-products not produced on purpose*: (e.g., contaminants of products or waste effluents released into air, water, soil, etc.). An example would be polychlorinated dibenzodioxins, which were never produced on purpose, but are nevertheless important pollutants (including being an inadvertent contaminant in 2,4,5-T).
    d. *Produced as a result of minimally controlled reactions.* (e.g., carbon monoxide from incomplete combustion).

5. Hazardous Wastes

Hazardous wastes often include **both**"used chemicals" (such as used solvents, metals, commercial products such as paints, and often polychlorinated biphenyls [PCBs]). They also often contain contaminant by-products (particularly troubling examples include chlorinated dibenzodioxins). *Complex mixtures* of a range of compounds are *often* encountered in hazardous wastes. Biodegradation, photodegradation, hydrolytic, fire-associated, and other products of chemical reactions among chemicals on site may also be included in the mix. *Across a hazardous waste site, multiple permutations may be encountered*. **Chemical analyses** are one way of assessing the presence of **some** of the compounds present. Such assays are best combined with **bioassays** to characterize the effects and to avoid grossly underestimating the hazards present.
Note: Because we typically provide domestic animals with a protected environment, clinical toxicoses related to hazardous wastes are rare in domestic animal practice.

6. Toxins and Toxicity: Definitions, Relative Potency and Toxicosis

Toxic: An adjective implying that a chemical has the properties of a poison = toxicant (see above).
Toxicity: A noun that refers to the amount of poison that, under a specific set of conditions, will cause a detrimental effect. It indicates the relative potency of the toxic compound.

Example: The toxicity of aldicarb is > the toxicity of carbaryl.
Usually agents are compared on a mg/kg basis; but toxicity can alternatively be compared on a molecule/kg basis.

Illustration:

Toxicant	M.W.	LD50 in mg/mouse	LD50 in molecules/mouse
Botulinus toxin	9×10^6	0.01	6.75×10^{12}
Tetrodotoxin	319	0.0087	1.63×10^{16}
DDT	352	6	1.03×10^{19}

Note: Toxicity is **not** the condition produced by the toxicant!!!
Toxicosis is the condition (*disease state*) produced by the toxicant.

7. Factors Influencing Toxicity
Route of Exposure
Form of toxicant - Examples:

1. In the past (and currently in certain other countries), leaded gasoline resulted in contamination of used motor oil with finely divided lead particles which were apparently much more highly bioavailable than equivalent amounts of lead objects. This waste oil often acutely poisoned cattle.
2. Barium sulfate is a poorly soluble salt and therefore has low absorption (low bioavailability) and is thus quite low in toxicity. This can be compared to barium chloride which is more soluble, more readily absorbed, and very toxic.
3. Particle size can influence toxicity. Compared to larger particles, small particles may more readily reach the lungs when inhaled or be absorbed in the gut when ingested; large particles in suspension may cling to hair and accumulate on the skin.
4. Lipid soluble compounds that are non-polar and non-ionized are more readily absorbed and moved across biological membranes than are polar, water soluble and ionized particles.

Animal factors

- **Breed or strain** (e.g., ivermectin more readily penetrates the blood brain barrier (BBB) of collies).
- **Age** (e.g., carbon monoxide - neonates are especially sensitive due in part to increase CO binding by neonatal hemoglobin).
- **Gender** (e.g., chlorpyrifos - bulls are especially sensitive due to testosterone influence on biotransformation to a toxic metabolite).
- **Stage of development** (e.g., teratogens, such as *Veratrum californicum* in lambs exposed *in utero*).
- **Physiologic state** (e.g., white snakeroot in lactating vs. non-lactating cows - excreted via milk protecting the lactating dam but putting the nursing animal at great risk).
- **Health at time of exposure** (e.g., **Bufo** toad poisoning is more hazardous to old animals with preexistent heart disease).
- **Individual variation**. Any population of the same species has a normally distributed variation in response to individual toxicants.

Environmental factors

- **Air circulation** (e.g., silo gases accumulate in confined spaces and settle to low spots).
- **Season, temperature** (e.g., fluoroacetate).
- **Light factors** (e.g., biological rhythms influence susceptibility, also photosensitization from poisonous plants or drugs develops only after sufficient exposure to UV light). Some toxicants readily photodegrade following exposure to bright sunlight.

Water factors

- **Quantity** (freezing, overcrowding, system or human failures).
- **Quality** (palatability, constituents including medications, salts, bacteria, algae, etc.).

Dietary factors

- **Nutrients**, their balance, (e.g., too little carbohydrate increases susceptibility of ruminants to urea toxicosis).
- **Contaminants** (e.g., natural toxins such as aflatoxin, feed additives such as monensin, and manmade toxicants such as pesticides may contaminate feed or food products).
- **Quantity** (e.g., too little feed increases tendency to ingest toxic amounts of poisonous plants, and also increases susceptibility to some mycotoxins. However, inadequate nutrition actually protects against toxic effects of some other toxicants that are bioactivated by enzymes in the liver, such as carbon tetrachloride).
- **Palatability** (e.g., toxicant may enhance or decrease palatability; or, alternatively, other foods present may mask toxicant).

Housing factors

- **Size** (influences crowding, ability to get away from a toxicant, stress, etc.).
- **Construction materials** (e.g., lead, PCBs, formaldehyde, etc.).
- **Heating and ventilation equipment** (malfunctions may set the stage for toxicoses from poisonous gases such as carbon monoxide or natural gas which contains methane).
- **Bedding materials** (e.g., *Juglans nigra*, black walnut shavings → laminitis in horses).

Miscellaneous

- **People** (Caretakers, children, visitors, other animals).
- **Other factors**

8. Toxicity Testing

Acute Toxicity Testing

- These tests assess the potential of a toxicant to cause adverse effects after a single dose or multiple doses during a 24-hour or shorter period.

Subchronic Toxicity Testing

- These assess the potential to cause effects after 30 to 90 days of repeated or continuous exposure.

Chronic Toxicity Testing

- These assess the potential to cause effects after prolonged exposure:
    - 1.5 years in mice.
    - 2 years in rats.
    - 3 or more years in dogs.
    - Included are tests for **carcinogenicity**.

Reproductive Toxicity Testing

- Evaluate the effects of the toxicant on:
    - Ovulation, conception, implantation.
    - Embryo and fetal development, length of gestation.
    - Parturition.
    - Lactation.
    - Early postnatal growth.
    - *Usually 2 or 3 successive generation (rat) studies are done*.

    - Males and females are exposed from 60 days before breeding until the end of gestation and lactation.
    - The offspring are dosed from weaning through their complete reproductive cycle, including lactation.
    - **Embryotoxic Vs. Fetotoxic Agents**: If an agent produces a stillbirth or *in utero* death, the correct term is *embryotoxic* if it occurs *in the embryonic period*, and *fetotoxic* if it occurs *during the fetal period*.

Teratogenicity Testing

- **Teratogen**: An agent which, when administered during gestation, produced *nonlethal structural or functional changes* in the embryo or fetus.
- Teratogenicity testing is usually separated from chronic reproductive toxicity tests.
- **Goal** is to administer the toxicant *during the period of* **differentiation** *of fetal organs and tissues*: e.g., mice exposed during days 6 to 15 of gestation; rats during days 6 to 18.

Mutagenicity Testing

- **Mutagenesis**: *Induction of changes in DNA*. This may include observable structural changes in the chromosomes, such as breaks, etc.
- But, changes in DNA are more often evident only at the biochemical level with no obvious structural alterations in the chromosomes. Most such changes are harmless change due to DNA repair, which is a common event.
- Note: Mutations are of concern because they can result in misreading the genetic code.
    - Genetic changes may be harmless (new peptide sequence works as well as the original version) or even beneficial (trial and error process --> evolution of the more successful).
    - However, evolution has already lead to considerable refinement; and mutagenesis is therefore generally undesirable. The primary concerns are that it may result in carcinogenesis or hereditary defects.
- **Four Types of Mutagenicity Tests** (commonly used for testing of chemicals).
    - *Dominant lethal test*: Males are treated with the test compound and females are examined for an increase in pre- and post-implantation losses.
    - *Cytological test*: Animals exposed to test compound - examine mutation susceptible cells (i.e., rapidly dividing cells of bone marrow, germ cells, etc.) for chromosomal aberrations.
    - *Ames Test*: Expose a mutant Salmonella bacterium that requires histidine for growth. If "back mutation" occurs, the organism grows in histidine-free media.Test compounds are often metabolically activated to a reactive form through exposure to liver cells, liver extracts, or hepatic enzymes.
    - *Host-mediated assay*: Animal is given both the *test agent* and the mutant *Salmonella* **ip**. Host may metabolically activate the compound which then causes the "back-mutation" in the *Salmonella* so that it propagates in histidine-free media.
- "Special Studies"
    - *Hemolysis tests*
    - *Irritation tests*: Well-founded controversy over tests done with known irritants which are nevertheless applied at high concentrations. Tests *in vitro* are coming on line to lessen the need to test commercial products for irritancy. Generally these can result in elimination of toxic components so that they do not need to be tested in animals. Final products are either formulated from ingredients already thoroughly evaluated in animal studies or are tested with animal irritations tests before manufacture and sale in quantity.
    - *Draize eye irritation test*
    - *Draize skin irritation tests*
    - *Other irritation tests*

9. Regulatory Toxicology
US EPA Registration of Pesticides

- EPA registration approval under the Federal Insecticide, Fungicide and Rodenticide Act means that the pesticidal product can be marketed and sold consistent with the label instructions and warnings.
- Registration confers an EPA registration number, e.g., 829 - 719, which must appear on all labels.
- Registration indicates that data supporting safe use has been submitted, reviewed, and approved by EPA.

- Registration indicates that the EPA has approved the wording on the pesticide label, as well as a confidential statement of the overall formula.
- Registration requires submission of toxicology and ecotoxicology data active on the ingredient (AI) and the formulated product.
    - Data requirements
        - Vary depending on the proposed uses.
        - Exposure assessment data include:
            - Environmental fate: Fate study requirements depend on the specific products produced and their toxicity (Data requirements may be lax).
            - Potential residue concentrations in food.
            - Applicator, worker exposure
        - Requires efficacy data: evidence that the product controls the target pests.
        - Efficacy information is presently waived for plant protection products in U.S.
            - View that market forces manage efficacy.
            - Efficacy data are critical component in other countries.
            - US EPA is focused on toxicity, but in other countries approvals are often granted by the Ministry of Agriculture.

Scope of FIFRA Registrations

- Plant protection products include:
    - Insecticides, herbicides, fungicides, and soil sterilants (biocides).
    - Plant growth regulators, gametocides, etc.
    - Not fertilizers.
- Animal treatments include products to kill flies, fleas, lice, ticks, mange mites, and other arthropod pests.
- Disinfectants and sterilants for use in or on:
    - Pools, water towers, and toilets.
    - Household surfaces.
    - Hospitals and animal hospitals
    - Food manufacturing, restaurants, public facilities, and hotels.

Biological Pesticides Include:

- Natural microbes.
- Genetically-engineered microbes that attack the pest.
- Insects that eat pest insects.
- Biochemicals:
    - Pheromones.
    - Repellents.
- Genetically-engineered plants.
    - Includes herbicide-resistant plants such as soybeans.
- Regulated by a different EPA division than that involved with conventional pesticides.
    - Requirements for approval (safety) are similar where possible. The approval process still relies on a hazard vs. exposure logic.
    - Methodology of assessment is different (microbes, proteins, DNA).

Labels of Registered Pesticides are a Legal Document and they Include:

- Precautionary statements - as warranted by the toxicity of the product and must list.
    - Signal word(s): e.g., Danger, Warning, Caution
    - First aid measures specific to the route of exposure: swallowed, inhaled, eyes, or skin.
    - Appropriate personal protective equipment: e.g., for applicators.
- Specific warnings: e.g., toxic to fish - do not contaminate water, etc.
- Ingredients statement:
    - Active ingredients, e.g.:
        - Pesticide(s)
        - Synergist(s)
        - Repellent(s)
        - Hormone mimic(s)
    - Inert ingredients

        - Vehicle
        - Wetting agents
    - Allowed application methods
    - Directions for use
        - Lists plants, animals, or types of places to be treated and time factors for application(s).
        - Includes preharvest intervals for fruits, vegetables, and grain crops, as well as forages.

Confidential Statement of Formula

- On file at EPA
- Identifies ingredients
    - Chemical names and the CAS No. as well as the EPA Reg. No. of specific components
    - Percentages of all active ingredients
    - Certified limits of concentrations of active ingredients and related compounds simultaneously synthesized, but not excluded during purification of the technical grade (final) product.
- Alternative formulations are sometimes listed.
- All are supported by analytical data on batches.

Types of Registrations

- Full approval.
- Conditional/time-limited approval.
    - Some data/assessment still needed.
- Emergency exemption
    - Temporarily allows a use to fight a special pest.
- Special local need.
    - Permanently allows use to address a small scale need.
- Experimental use permit (EUP).
    - No approval is required for small-scale tests intended only to determine a pesticide's efficacy, e.g.:
        - Less than 10 acres treated
        - Food does not go into commerce (crop is destroyed)
    - For larger scale experimental uses, an EUP is required.
    - EPA reviews a subset of the data normally required for a full approval in order to consider whether to issue an EUP.
        - Includes metabolism and fate in animals and the environment and animal toxicity as well as the acute ecotoxicity of the product.
        - Often these data are submitted for an EUP 1 - 2 years before an application is submitted for full registration.
        - A 12 to 18-month review time is typical for an EUP.
        - An EUP may involve a request for temporary tolerance levels of the pesticide in food.

Financial Investment to get a Newly Synthesized Pesticidal Compound to Market Based on an Industrial Survey '89 - '94

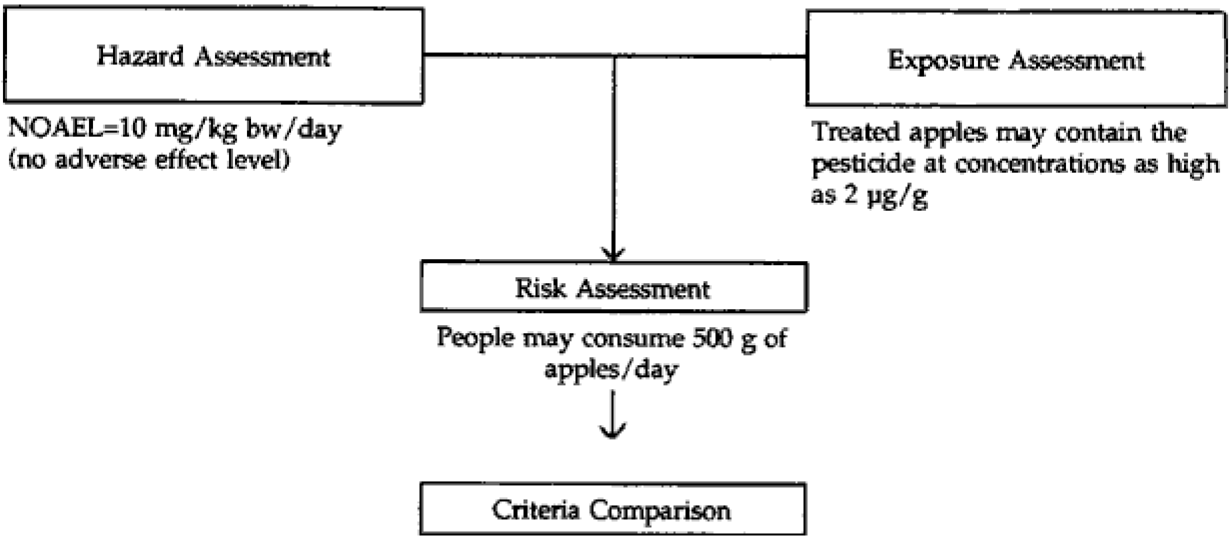
- Development costs average 32 to 70 million dollars.
- Time: Often it takes 8 years from discovery of a new compound to first sales; yet patents last only 12 years from the time of submission to the U.S. patent office.
- Approval by EPA typically takes 2.5 - 3.5 of the 8 years.
- EPA fees average $140,000.
- Cost for pesticide approval is still **much less** than for approval of a drug (by FDA), because there is no EPA requirement for clinical trials.
    - Drug substance approval by FDA may cost: 200 million dollars or more.

Registration is Evergreen (it is often an ongoing process)

- Initial approval for an active ingredient typically involves one formulation for use on one crop but:
    - Usually uses are expanded to other crops.
    - Usually additional formulations are developed.

    - May include combinations with other active ingredients (to increase the spectrum of pest species targeted).
    - May include formulations suited to different types of application equipment) sprays, granular products, seed-coating products, etc.).
- EPA may add to the data requirements depending upon reports of problems in the field and/or new regulations.
- Re-registration has been an ongoing process since 1988.
    - Re-registration includes a periodic review of files.
- EPA may require additional field or laboratory data to supply missing information for any existing or newly registered pesticide.

Logic by which the EPA Decides on a Safety Issue:


Hazard Assessment
Exposure Assessment
NOAEL=10 mg/kg bw/day
(no adverse effect level)
Treated apples may contain the pesticide at concentrations as high as 2 µg/g
Risk Assessment
People may consume 500 g of apples/day
Criteria Comparison

For example, asks whether there is a 100-fold safety factor. In other words, is the exposure at least 100-fold less than the NOAEL? Note, this level frequently is considered to be the allowable daily intake (ADI) except in the case of carcinogens.

EPA Uses a Computer Model for these Types of Dietary Risk Assessments Which:

- Contains food consumption data by age group and geographic location.
- Assumes the concentration present is at the tolerance level for all crops for which the product is approved.
    - As a rule, this would be higher than actual concentrations present since a tolerance concentration is the maximum allowed.
    - The model can be refined with actual residue and market share data when they are available.
- Exposure is considered to be the sum of contributions of the pesticide from all sources.
- This is compared to the "Reference Dose" (RfD) (may be set at 1/10 the maximum tolerated dose allows for exposure by all routes) as well as to the Allowable Daily Intake (ADI). The RfD is not expected to cause an adverse effect despite a lifetime of exposure.

Tolerances

- Specify allowable pesticide residue concentrations in foods and feeds.
- Tolerances are based on residue data, toxicity data, and the ADI. Each tolerance is specific as to the crop, product formulation, and timing (of use).

Delaney Clause

- Prohibits any detectable amount of carcinogenic additives (includes pesticides) in processed foods.
- The Delaney Clause pertains only to carcinogens. Recently approved legislation changed the law so that the EPA will use a risk/benefit analysis similar to that typically applied in other health risk decisions.

    - However, unlike the typical 100-fold safety factor, the EPA will generally allow a "negligible" (e.g., 1 in 1 million lifetime) excess cancer risk.

Farm Worker Safety

- Compares exposure levels expected with recommended use(s) to NOAEL doses in laboratory animals.
    - Usually use the 28-day or 90-day NOAEL from rodent studies.
- Computer models/databases are used initially.
    - Consider typical exposures to active ingredient.
    - Commonly use a 100-fold safety factor.
- Other data may be required from studies of:
    - Field deposition.
    - Skin penetration.
    - Biomonitoring for exposure and/or effect, for example:
        - Urinary excretion of the pesticide or a metabolite (a measure of exposure).
        - Cholinesterase inhibition (e.g., for organophosphorus or carbamate insecticides) (a measure of effect).
- Personal protective equipment to be worn by workers at specific times.
    - Clothing.
    - Gloves.
    - Masks.
- Restricted entry interval.
    - Time after application before workers can enter the treated field.

EPA Environmental Toxicology Testing Protocols

Species to be evaluated may include			
Birds	**Fish**	**Invertebrates**	**Plants**
Mallard	Bluegill	Eastern oyster	Green algae
Bobwhite	Rainbow trout	Daphnia magna	Blue-green algae
Includes avian reproduction tests	Sheepshead minnow	Penaeid shrimp	Diatom
-	Includes early life stage tests	Grass shrimp	Duckweed
-	Includes bioconcentration in fish	Honeybee	-

Note: The tested species may be used to estimate the susceptibility of all other species and even to consider whether interspecies effects are likely. Interspecies effects may include: impairment of predator avoidance and thus an increased impact of predation; decreased effectiveness of a predator; immunosuppression; etc.

10. Definitions and Terms used in Toxicity Testing, Regulatory Toxicology and in Comparing Toxicants

Values for the terms listed below (i.e., mg of toxicant/kg of BW) pertain to the *species and strain of animal, as well as the route of administration tested*. They are often used for extrapolation in considering the potential hazard to other species such as man.

TD = toxic dose

TDL = toxic dose low: lowest dose that produces an adverse effect and, by definition, 2 x the TDL = a nonlethal dose.

HNTD = the highest nontoxic dose: the largest dose that does not exert a detrimental effect.

NOAEL = similar to HNTD. NOAEL: the "no-adverse-effect" (no detected adverse effect) level from a specific study, except that the NOAEL is more often used to refer to repeated, e.g., lifetime, exposures.

RfD = Reference dose: the highest dose expected to have no effect on the species of interest (often human beings) despite a lifetime of exposure. The RfD may be set at 1/10 of the HNTD or 1/10 of the NOAEL.

TDH = toxic dose high: a dose that will produce an effect and 2 x this dose is a lethal dose.

LD = lethal dose.

LD_{LO} = lethal dose low: lowest dose that produced deaths in animals during the period of observation (sometimes expressed as LD_{min}).
Often percentages are attached to the LD to indicate the fraction of the animals that would be expected to die from a given dose.

LD50 = median lethal dose. This is a calculated dose that is projected as being likely to cause death in half of the exposed animals of the species/strain/age/sex exposed. Thus often times, many animals would still be expected to die at doses less than the LD50.

LC = lethal concentration. It pertains to lethal concentration of a toxicant in feed, water, soil or other "matrix" to which the animals are exposed. As in the case of LD, various percentages are attached to indicate the fraction of the animals expected to die.

TC = toxic concentration. Toxic concentrations relate to the first recognition of a toxic effect. The specific (threshold) toxic effect(s) should be identified when a toxic concentration is given.

MTD = maximum tolerated dose. It is sometimes used to indicate maximum tolerated dose (highest dose not causing death). Other times it is used to indicate minimum toxic dose (lowest dose causing any abnormality). Thus, it is best to ask what is meant by MTD.

ED or **EC** = imply effective dose or effective concentration. These terms are typically applied to drugs or feed additives. Percentages are used to indicate the fraction of individuals of the test species/strain/age/sex expected to respond.

Other Terms used in Comparing Toxicants

Chronicity factor = the ratio of the acute LD50 to the chronic or 90 day LD50.
May be influenced by the **tendency to accumulate vs. being rapidly eliminated or detoxified**.
May be influenced by cumulative damage that occurs from **repeated toxic insults** to a target tissue.

> e.g.: *Warfarin* - on a repeated basis is more toxic to dogs than on a single dose basis.
> Chronicity Factor (Warfarin) = (Acute LD50) / (90 day LD50) = 1.5 mg/kg / 0.08 mg/kg = 18.75
> Therefore, the C.F. for warfarin is approximately 19.

Many toxicants do not accumulate or have much of a cumulative effect.

> e.g.: C.F. for *caffeine* = 1.3.

Toxicants with a C.F. > 2.0 are considered relatively cumulative

Some toxicants induce a degree of tolerance in the animal when it initially receives low doses.

> e.g.: *Potassium cyanide*: The acute LD_{50} is 10 mg/kg, but pre-exposed animals tolerate 250 mg/kg.
> Therefore, the C.F. for KCN = 0.04.

11. Hazards, Risks, Risk Assessment, Risk Management

Hazard

The *likelihood* of poisoning *under the conditions of usage* and the *probability of exposure*.

- Thus, hazard is not the same as toxicity!
- Toxicity is the ability of a given dose to have a particular effect, but **hazard also considers the likelihood of a person or animal ever being exposed to that dose**.

- Hazard depends on: volume available, concentration, location, use restrictions, label warnings, users allowed access, and many other factors.

Risk
An *estimate* of the likelihood of adverse effects assuming that a chemical exposure of a population has occurred.

- Risk is expressed in terms of the *estimated frequency* of a problem in the exposed population (*i.e., one in a million*)....
- ....*or in terms of relative risk*, that is, the **probability of a disease in an exposed vs. an unexposed population** (i.e., *twice the rate of the unexposed population*).

Risk Assessment is comprised of stages including

- **Hazard identification** - which asks whether a particular chemical can cause an adverse health effect.
- **Dose-response evaluation** - which considers the relationships between dose and the incidence of the adverse health effected in the population. Considers thresholds, shape of dose-response curves, etc.
- **Exposure assessment** - involves estimation of level and uniformity of exposure of the population.
- **Risk characterization** - the last stage involves a prediction of the frequency and severity of effects in the exposed population.

- When 95% confidence limits are given in the risk characterization, you have an idea of the reliability of the prediction.
- Note: **Risk assessment involves currently evolving methods**. There are a large number of assumptions typically involved and there can be considerable differences in the calculated risk depending upon these assumptions and the risk model employed. An astute risk assessor states the assumptions used and attempts to indicate their level of confidence in the risk calculation.

Risk Management

- Regulatory agencies often isolate risk assessment from risk management. The latter pertains to the measures taken to reduce risk. In toxicology, this is commonly focused on reducing exposure of the population of concern.
- Environmental cleanups at waste sites may rely upon bioremediation, vitrification, mechanical removal and incineration, capping, soil incineration, water pumping and activated carbon binding or "air stripping."
- In veterinary practice risk management may involve changing the feed and water or removing animals from the site until the source of exposure is known and eliminated.

Editorial - re Human Frailty: *Murphy's law is the rule.*

- Because of Murphy's Law, whenever possible, it is best to try to develop "human-proof" products. Otherwise we are forced to live with the consequences of human frailty, which often means unnecessary poisoning!

12. Dose-Response Relationships: Types, Terms, Calculations, LD50s, and Therapeutic Index

Dose-Response: "The most fundamental and pervasive concept in toxicology".

- All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy. - Paracelsus
- It is only the degree of exposure necessary to cause an adverse effect that separates the "toxic" from the "nontoxic" and the "essential" from the "lethal."
- "There are no harmless substances. There are only harmless ways of using substances." - Emil Mrak.

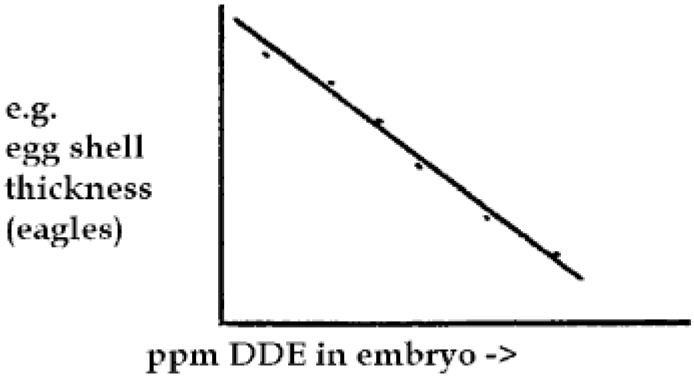
Definitions
***Dose-response**: Relationship between the **level of exposure and the magnitude of the response**.*

- Much of veterinary toxicology.... deals with levels of exposure that are within ranges reflected in previously generated dose-response data.
- Risk assessment (for human safety) commonly deals with extrapolation **below** the experimental range.

- Risk assessment (for animals in ecosystems) commonly deals with exposures in the experimental range, but *extrapolation is necessary to a range of untested and phylogenetically diverse species*.

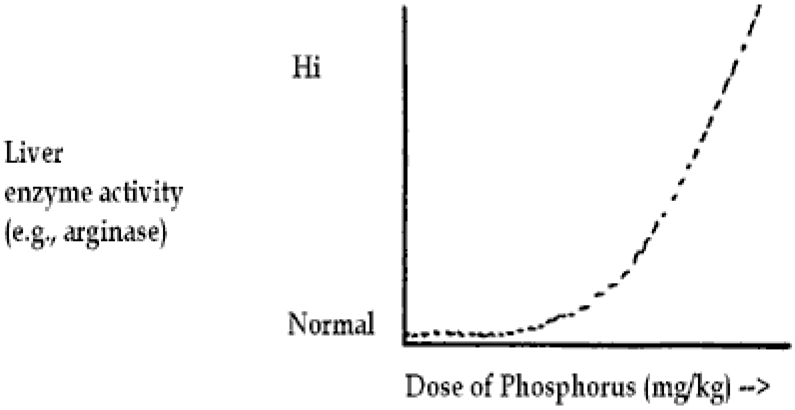
Types of Responses - Graded as Contrasted to Quantal Responses

Graded data = varied in intensity, e.g., enzyme activity, heart rate, graphical example: egg shell thickness in eagles.



Graded dose-response data can be analyzed by regression analysis, to identify linear or curvilinear relationships.

Graded dose-response data (a second example).



Quantal data = + or - e.g., lethality.

Quantal data (examples)

% dead vs. alive (lethal dose = LD).

% showing an increase in heart rate to 100 (a toxic dose = TD)

% showing control of seizures (effective dose = ED).

One can plot quantal responses of a group of animals vs:

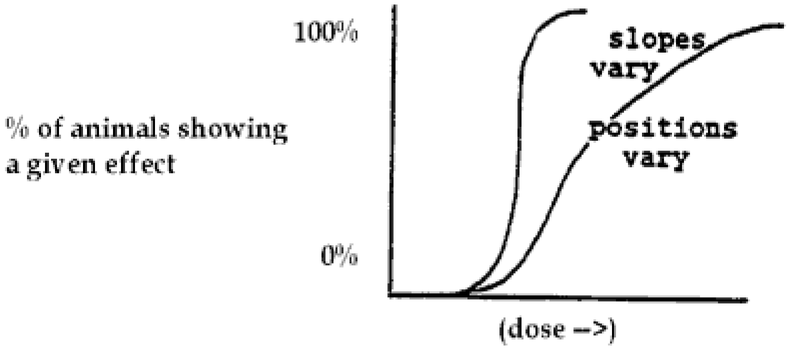
Dose.

Concentration in air.

Concentration in feed.

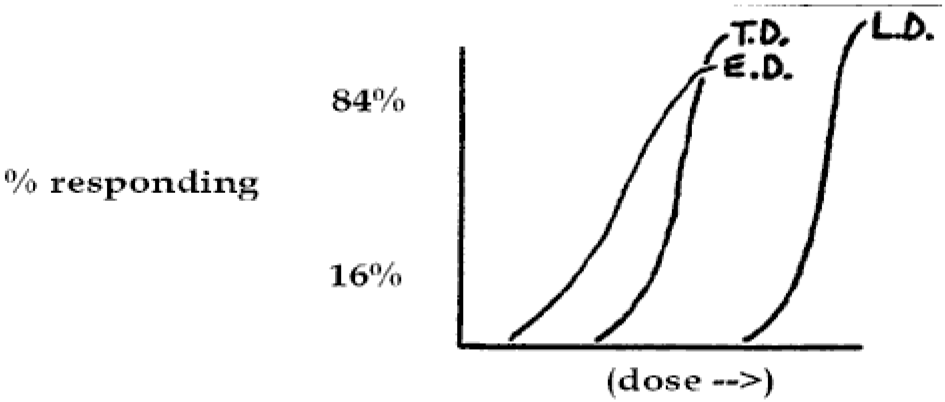
Frequency of administration.

Dose-response curve for a quantal response (example)



The steeper the dose-response curve, the more uniform the response among the test animals (i.e. more of them respond within a narrow dose range).
The flatter the dose-response curves, the greater the variation in response to the doses given. With flatter dose-response curves, it is much more difficult to predict the effects of a given toxicant dose on a given animal.

Different shaped curves for different responses may also occur (example).



Therapeutic Index (TI) applies to pharmaceutical agents and is the ratio of the median lethal dose (LD50) to that producing a desired median therapeutic response ED50.

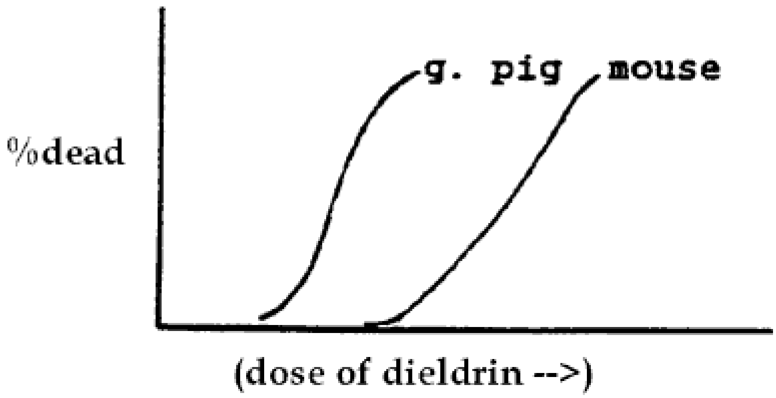
e.g. $\frac{LD50}{ED50}$

Depending on which values are used to calculate the therapeutic index the TI value will differ widely, therefore, be sure to know the basis for each therapeutic index.

Standard Safety Margin. Another useful calculation is the Standard Safety Margin, which compares the lowest lethal dose (LD1) to the highest effective dose (ED99), giving a much more conservative evaluation of safety of a product.

SSM = LD1/ED99

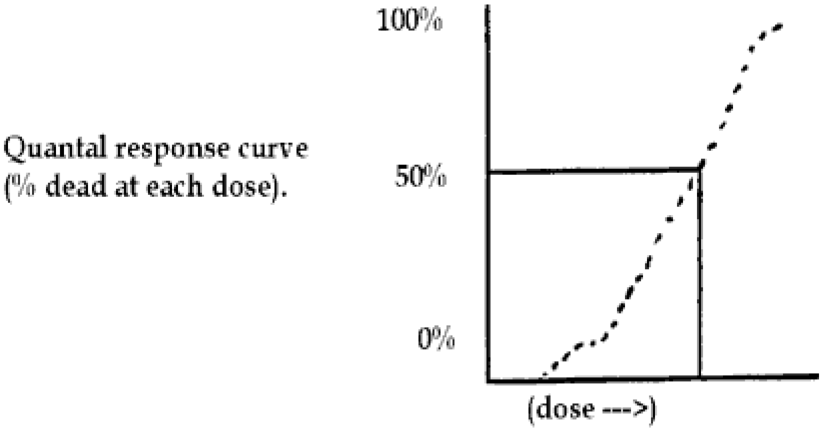
Species differences in dose response



LD50: Primary advantage is that it is generally the most reliable number (regarding the probability of a lethal effect that you can get).

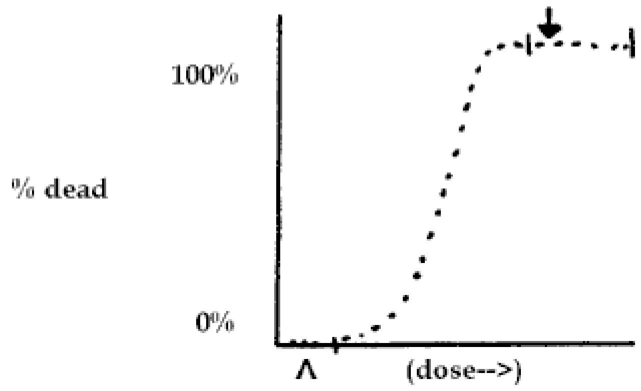
- "Better than nothing" when estimating outcome of an exposure.
- Used for extrapolation.
- Disadvantages: Tells you nothing about shape or slope of dose response curve. Thus, you still know nothing about LD1 or the lowest toxic dose.
- LD50 bears no relationship to long term toxic effects

Derivation of an LD50
(same principles apply to other types of quantal data, e.g., ED50, ED99, TD1)



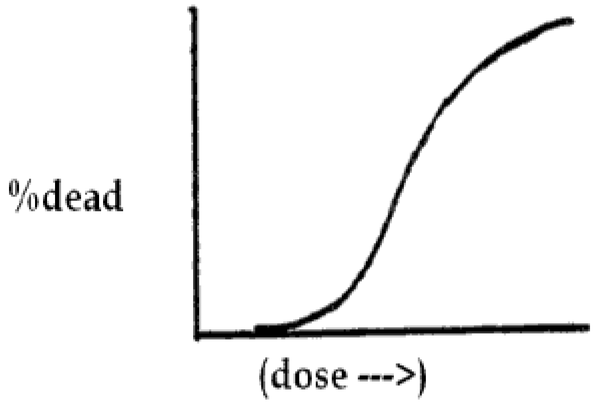
If 50% died at a single dose, it could be termed the LD50. However, it can be a problem to hit exactly 50% dead; and trial and error is inefficient - too many animals used, too many experience the toxicosis.

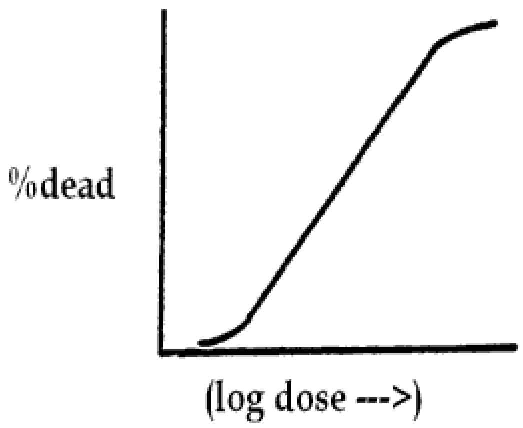
Doses with 0% or 100% dead are no help in ID of the LD50.



Reason, *they do not tell you anything about the dose-response curve*. *At 0% or 100%, you could be anywhere on the curve below the LD1 or above the LD100, respectively.* So avoid these doses.

To improve accuracy in extrapolation to arrive at an LD50, it helps to straighten the curve by **conversion to a log dose**.





Using semi-log/probit paper, the method of Miller & Tainter is relatively simple.
The log of the dose is plotted vs the percent surviving to derive the sought probit (probability unit) value from the left side of the graph paper.

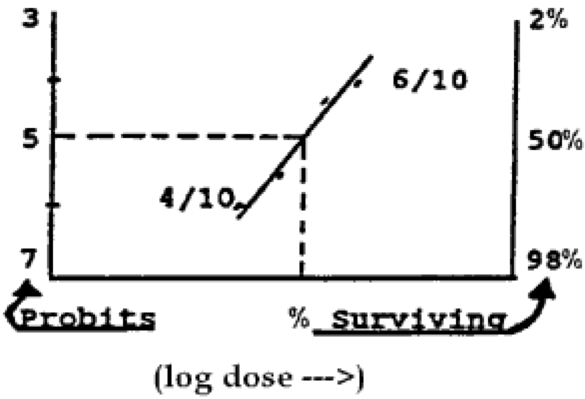
The Miller and Tainter Method also gives the **standard error (SE) of the LD50** through the use of probits (probability units).

The difference between the dose at probit 4 and that at probit 6 is equivalent to ±1 standard deviation = 2S.

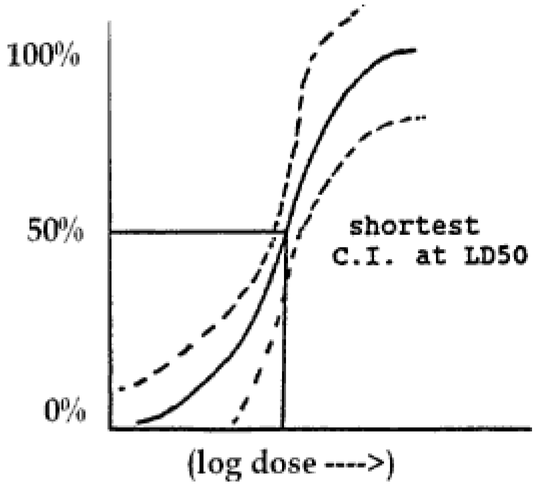
and SE = 2S

2N'

where 2N' = the number of animals tested between probits 6.5 and 3.5.
Thus one can derive an LD50 (or ED50) + its SE.



The **Weil Method is more complex, but it gives the 95% confidence interval (CI) of the LD50**. Advantage: By examining this CI, one gets an idea of the reliability of the reported LD50 value. The assumption is that, if a series of experiments were performed, the actual LD50 would be within this range of calculated values (the so-called confidence interval) 95% of the time.

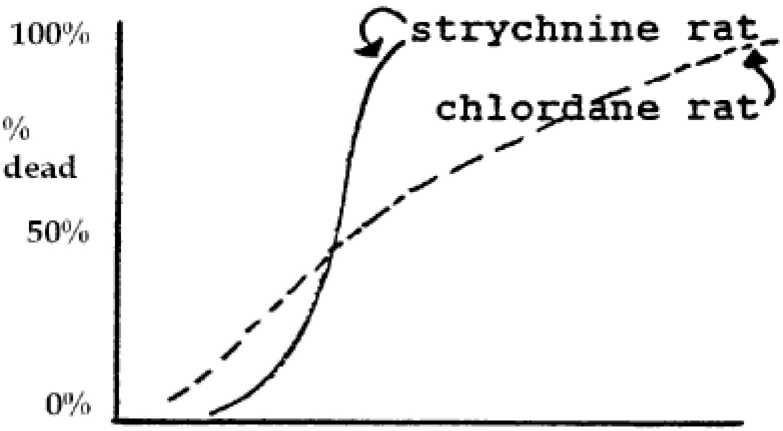


Because CIs tend to be smallest in the midrange where you have a larger number of both responders and non-responders, LD50s are among the most reliable predictors of lethal toxicity. Similarly, it is difficult to predict reliably the minimum lethal dose (LD1) with very much "confidence." It has been stated that to be "certain" of an LD1 "with confidence" of being correct (or an LD99) would take approximately 25,000 rats.

Note: ***In a clinical setting, a veterinarian would not want the exposure of the patient to approach the LD50 before being concerned about the likelihood of death (to say nothing of potential organ damage).*** Typically, it is necessary to extrapolate from laboratory rodents to domestic animals. Even within the same species, considerable variability would be expected.

The same considerations are true for ED50s, TD50s, TD1s, etc. Unfortunately, however, acute toxicity data other than the LD 50, and chronic toxicity data are often time consuming or difficult to obtain...or they simply do not exist. Thus, you may find yourself working with an LD50 number and hoping that it gives you a rough idea of the lethal hazard in another species with which you are working.

Importance of Knowing the Shape of the Dose-Response Curve

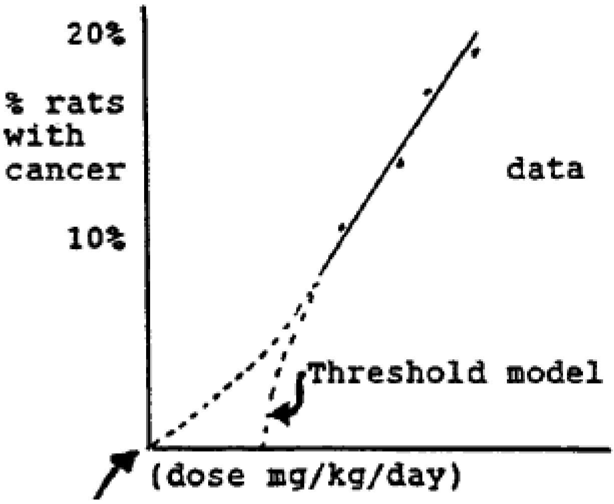


Compare LD50 alone, assume same toxicity...
Compare LD80s, chlordane looks less toxic...
Compare LD10s, strychnine looks much less toxic.

Unfortunately, you rarely know the shape of the dose response curve in laboratory animals, let alone domestic species.

13. Risk Assessment Revisited

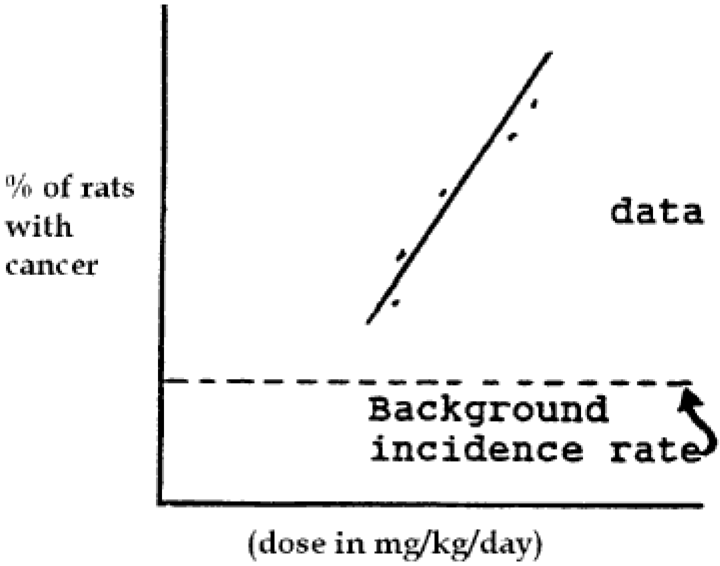
In toxicity testing to ensure human safety, it is usually necessary to extrapolate below the experimental range.



One-hit model (conservative)

Problem: which model is most accurate......
the one-hit or the threshold model?

When the background incidence of a given problem is high in the test species, subtle increases in risk can be hard to detect.



Problem: What is an acceptable risk?

- Depends on benefit and alternatives.
- Risk/benefit ratio
    - cars
    - planes
    - chemicals
- **One expects risk, but not because of intentional or ignorant actions** , e.g., dumping of "waste oil" (PCBs) on roads.
- **People tend to accept risks more readily when they are well informed about them**, e.g., the risk associated with the uses of automobiles vs. a risk associated with a food additive thought to be "safe".

Reducing Chemical-Associated Risk
Alternative technologies - sometimes appropriate

- **Changing synthetic methods** to produce compounds of greater purity with lesser degrees of contamination.
- **Replacing** a commercial chemical product with a formulation that poses a reduced risk to the public or the environment. The alternative may be more or less expensive than the older technology.
- **Proper disposal** rather than improper disposal. Sometimes burning at a high temperature can be used to convert a toxic organic compound to its constituent minerals (i.e. CO_2 and water, and perhaps some salts).
- Another alternative may involve **recycling a toxic waste chemical** to be used as a precursor chemical in another manufacturing process rather than disposing of it into a stream. This may result in a higher or lower cost for the final products.

Ethics of the situation
Sometimes, a company may not adopt the newer technology even when a product is much safer and the increase in cost is minimal, and thereby they may be able to have a less expensive product that competes effectively in the marketplace or that provides higher profits to the company and the shareholders.

14. Toxicokinetics

Definition: Relationships between tissue concentrations of a toxicant and time.

Differences from pharmacokinetics:
In clinical toxicology cases one deals with:

- Potential poisoning (not yet absorbed).
- Actual toxicoses (altered physiology/may alter kinetics over time).
- Residue contamination of foods such as meat, milk, or eggs.

Whether the problem relates to poisoning or residues, toxicokinetic data may be used either:

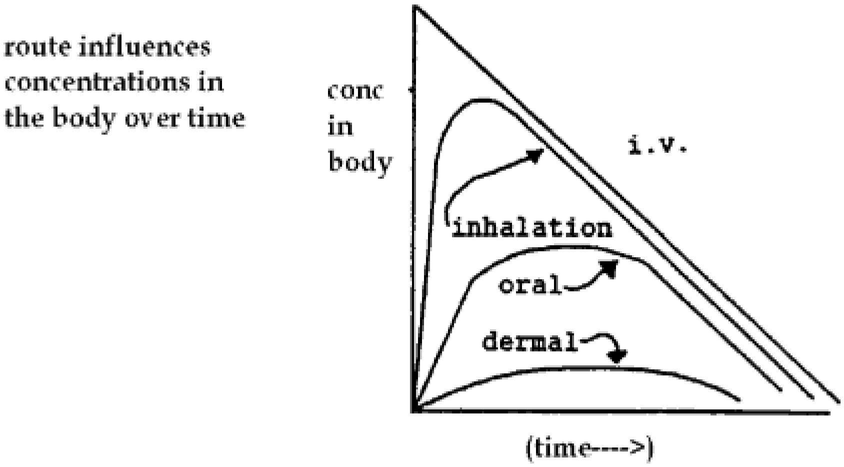
- to predict "normal" rates of metabolic change (activation or detoxification) and/or elimination, or
- to choose methods to help decrease the toxicant concentration at the receptor (e.g., to limit absorption, or increase detoxification or excretion).

As compared to typical uses of therapeutic drugs, in toxicoses, kinetics are more likely to be altered by:

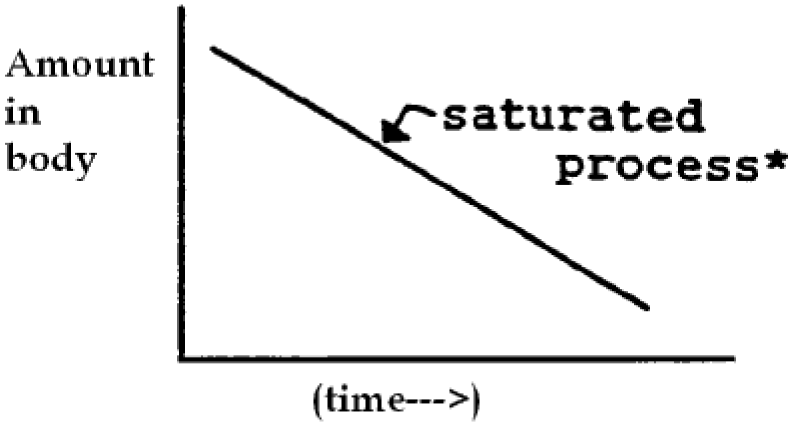
- *Saturation of enzymes* involved in metabolism (detoxification or toxification) or of enzymes employed in carrier systems necessary for elimination
- *Organ system dysfunction or failure*

e.g. toxicant-induced liver or kidney damage that alters metabolism and/or elimination of the toxicant
e.g. circulatory problems resulting in hypotension secondary to shock
e.g. acidosis due to exertion and seizures

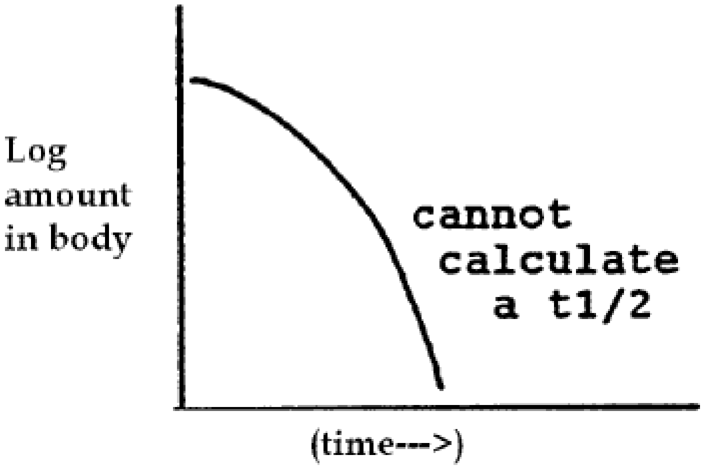
Review of some important kinetic concepts.



Zero Order (sometimes termed as "Michaelis-Menten kinetics").

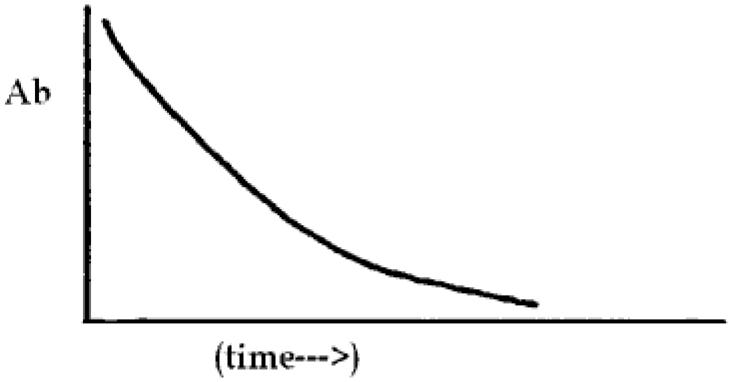


**Saturated process, therefore proceeding at maximum amount that the body can handle per unit time (i.e., n mg/unit of time).*



Reason Zero Order
Ab(t) = starting Ab - x t Ab
Where Ab = amount in body.
Ab(t) = amount in body at time t.
x = amount elim. per unit of time (x has no exponent, and therefore is zero order).
t = time (after dosing).

First Order Kinetics
The usual situation for most drug and other toxicant exposures.



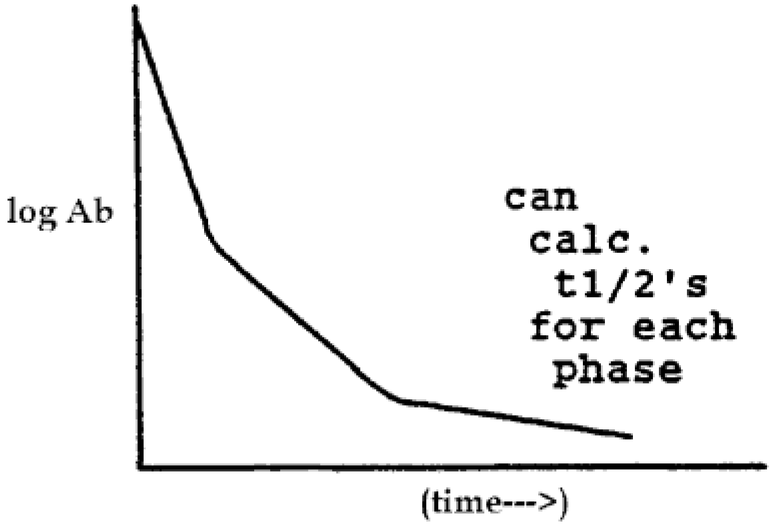
Rate of process may be limited by blood flow through liver or kidney; e.g., if all or a fixed fraction of the compound is cleared on each pass.

Early on: Rapid fall in amount in body. Later on, rate of elimination slows as blood concentration gradually declines.

Reason first order = first order exponent:
Ab(t) = Starting (e^{-kt}) Ab
Where
e = 2.72 = base of natural logs.
k = rate constant (= fraction elim. per unit of time).

Note: Kinetics may change from zero order (process saturated) to first order (no longer saturated).

More complex models may explain the disappearance of some xenobiotics, e.g., two or three compartment models.



In residue cases, one may be most interested in the terminal (elimination) phase, but ignoring the earlier phases may lead to an overestimation of the time necessary to clean up the animals.

Kinetics are influenced by the basic chemistry of the xenobiotic:
Bioavailability of xenobiotics varies from 0% to 100%. The rate of absorption, metabolism and/or elimination depends on chemical size and structure, fat solubility, and ability to interact with degradative enzymes, carrier systems, and alternative binding sites.

- e.g., Ca^{++} uptake system in the gut also takes up Pb^{++}.
- e.g., Organic acids often are excreted by an active process in renal tubules (e.g., 2,4-D).
- Highly fat-soluble compounds that resist biotransformation increase in fat over time. With chronic low level exposure, biomagnification occurs (biomagnification is the redistribution to the fat in this case) (e.g., heptachlor epoxide).

Biotransformation
Although there are some exceptions, with biotransformation, the toxicant usually becomes more polar, and therefore less lipophilic and more water soluble.
→ Protein binding tends to be less
→ Storage in fat tends to be less
→ Resorption across biological membranes (renal tubules) tends to be less
→ Renal elimination tends to be accelerated

15. Biotransformation processes
Phase I:
- Oxidation
- Reduction
- Hydrolysis

Phase II (conjugation) compounds may be hooked to:
- Glucuronate (glucuronidation). Increases water solubility
- Amino acids (glycine, etc.) Increases water solubility
- Glutathione (abbreviated GSH = a tripeptide of glycine, glutamic acid and cysteine). After GSH conjugation, glycine and glutamic acid are cleaved off and an acetyl group is added to form an acetyl-cysteine derivative of the xenobiotic and this form is typically excreted by the body. Another name for such an acetyl-cysteine derivative is a mercapturic acid. GSH is a low capacity system that is essential for preventing excessive oxidation of intracellular molecules. Conjugates (both GSH conjugates and mercapturic acids are typically much more water soluble than the parent xenobiotic.
- Sulfate (sulfation). Makes more water soluble
- Acetate (acetylation). Usually makes more water soluble
- Methyl groups (methylation) (can make more volatile sometimes increasing excretion via the lungs, but also can make more lipid soluble).

Diagnosis and Management of Toxicoses

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1. Antemortem Diagnosis

The diagnosis of toxicological diseases on the basis of signs alone is not only very often difficult or impossible but may be dangerous as well. Each body system can react in a limited number of ways, producing clinical signs, and there are thousands of toxic agents that may affect these systems. In addition, when a clinician observes an animal with signs of illness or poisoning he may see only one phase of the syndrome. Toxicological diseases may be acute or chronic, and the clinical presentation will vary depending upon the route, extent, and frequency of exposure; the species involved; the time elapsed since the most recent exposure; and many other factors.

A confirmed toxicological diagnosis often rests upon appropriate findings, including: a) exposure history, b) clinical signs, c) time of onset, d) duration of effects that are compatible to the toxic potential of the agent involved, as well as e) detection of the toxicant in the animal to confirm exposure (e.g., blood Pb), and in some cases, f) specific evidence of pathophysiologic derangement (e.g., acetylcholinesterase inhibition).

Even when an individual animal may no longer benefit from laboratory confirmation, positive or negative laboratory results may ultimately protect other animals or humans from toxic substances or missed diagnoses. Many specific antidotes have inherent toxicity, and their use in unconfirmed cases of poisoning can sometimes be hazardous. Also, clinical signs alone are not considered determinative evidence when presented in court. Therefore, efforts to obtain a specific diagnosis constitute time well spent.

The 5 basic routes of exposure to poisoning are: ingestion, cutaneous (topical), inhalation, injection (or envenomation), and ocular. Most toxicoses result from the oral ingestion of a toxicant, but some chemicals including many insecticides, phenols, and other lipophilic substances may also be efficiently absorbed through intact skin. Abraded skin may absorb some substances that otherwise might not reach toxic concentrations following dermal exposure. Of course, many volatile, aerosolized, or even solid particulate agents may be absorbed from the respiratory tract. For most agents, the rate of absorption is injection > respiratory > oral > topical. The route of exposure often influences the choice of specimens for confirmation. In addition to toxicosis due to systemic absorption of a compound, many compounds (e.g., corrosives) may result in direct tissue damage.

Identifying the Source

When poisoning is suspected, efforts should be made to determine the possibility and likelihood of exposure. Encourage the client to look in all places to which the animals have access. Be persistent and have them contact you after the search. If on a house or farm call, look with the client. If suspected toxicants are found, they should be saved for laboratory submission. When containers are found, read the ingredients list and any antidotal procedures (bearing in mind that some labels are out of date with regard to treatment recommendations). When toxic plants are suspected and there is evidence of significant consumption, be sure to get specimens for identification. Plants may be wrapped in wet newspapers and placed in a plastic bag prior to shipment (preferably with cold packs) to the laboratory or to a local botanist for identification.

Specimens from Animals

Care to avoid cross contamination of any sample by a potential toxicant is absolutely essential. It is therefore advisable to obtain specimens from animals before handling suspected source materials. If at all possible, before treatment is begun, refrigerate specimens of whole blood (10 - 20 ml with calcium EDTA as the anticoagulant) and freeze samples of serum (10 - 20 ml). Smaller specimens may be sufficient for certain tests. Volumes obtained may be reduced in particularly small species/individuals. In addition, save liberal portions of vomitus, urine, and feces for laboratory analysis. If vomitus cannot be collected and if gastric lavage is indicated, the initial lavage washings (using water only), should be submitted. The vomitus or lavage washings should be frozen in a tightly sealed jar. If topical exposure is suspected, hair may be frozen in a sealed container and submitted for analysis.

Feed and Water

When feed contamination is suspected, representative specimens of the material being consumed immediately prior to the onset of apparent toxicosis must be obtained. Delays in securing such samples may result in continued exposure to the toxicant and the subsequent absence of remaining feed for toxicologic analysis. For dry concentrate feedstuffs, obtain 2-kg samples of a composite from several areas of the incriminated feed. If moisture concentration is 13% or less, such feed can generally be shipped with no special method of preservation. Higher moisture feeds and forages should be kept frozen prior to and during shipment to the laboratory. When volatile substances are suspected as feed contaminants, however, the feed should be placed in clean glass jars and tightly capped and frozen. Water specimens may be similarly preserved and, if not filled more than 2/3 full, usually tolerate being frozen (in a tilted position) prior to shipment. In attempting to determine an antemortem diagnosis, one must remember that only a few toxicological tests can be done on a "stat" basis by most laboratories, e.g., blood lead, acetylcholinesterase. Due to the difficulties in chemical analysis for many toxicants, delays in receiving results of days to weeks must be anticipated. Serum chemistry, serum electrolytes, and other clinical diagnostic tests may rapidly contribute to a specific diagnosis (e.g., hypercalcemia in cholecalciferol toxicosis).

2. Postmortem Diagnosis

At necropsy it is **essential** to obtain a complete set(s) of specimens for chemical analysis and a complete set(s) of tissues for histopathology and other (e.g., bacterial and/or viral) studies. **Many toxicologic diagnoses rely not only on residues of the toxicant but also on compatible lesions and/or the absence of evidence of other diseases** capable of causing similar clinical effects. Specimens for analysis should be **individually** frozen and double bagged (with a paper label marked in pencil between 2 tightly sealed Whirl-Pack bags). The following specimens should be **routinely collected**: stomach or rumen contents, intestinal contents, feces, 1/2 of the brain, liver (without the gall bladder or bile contamination), kidney, body fat, and urine. Specimens should be large (i.e., up to 250 grams of stomach or intestinal contents, parenchymal organs, or body fat). In case of dermal exposure contaminated skin should be bagged, frozen, and submitted. In such cases, specimens of internal organs must not be contaminated from contact with the skin. Repeated cleaning or changing of instruments and gloves may be desirable after the skin has been reflected from the animal. Similar concerns exist when higher concentrations of toxicants may be present in the gastrointestinal tract than in organs for analysis.

3. Management Introduction

Goals for the management of acutely poisoned animals are ordinarily addressed in the following sequence: first **-stabilize vital signs**; second-clinical evaluation; third-prevent continued exposure to the toxicant; fourth-administer an antidote if available; fifth-facilitate removal of the absorbed toxicant; and sixth-supportive therapy and observation. Different antidotes counteract the effect of toxicants in various ways. Many "antidotes" are directed toward achieving stabilization of vital signs, decreasing exposure, or facilitating removal whereas other "antidotes" specifically antagonize the toxicant at a primary or secondary site of action. The **excessive** reliance on an antidote's action can be dangerous.

Often treatment of a patient must begin before a diagnosis is clearly established. The vast majority of toxic substances do not have specific antidotes, and even when an antidote can be used, the patient will often benefit equally from supportive therapy, which offsets the toxic effects on the animal. In either case logical steps toward preventing further absorption and detoxification of the animal are usually of **substantial** value.

It is wise to caution animal owners regarding hazards from human exposure to toxic substances (on the skin, in vomitus, in the environment, etc.) as well as animal kicks or bites. Keep in mind that a poisoned animal may no longer perceive or react to its owner in the usual way. Acutely ill animals that can be seen immediately should not be treated at home. Removal to the veterinary facility or a separate holding pen should be used to separate the animal(s) from potential environmental sources. A **change of food and water** is often recommended until the source of the toxicant is known.

4. Stabilizing Vital Signs

The objective is to preserve the life of the animal regardless of the etiology, buying time for detoxification to occur and for specific antidotes to have their pharmacological action. When multiple animals, e.g., herds, flocks, kennels or catteries, are involved, a system of triage may be necessary. Careful medical managements including restoration of fluid and electrolyte balance and maintenance of adequate respiratory function is associated with a higher survival rate than reserving treatment until "heroic" measures are necessary.

a) Maintenance of Respiration

It is important to emphasize the needs for: 1) a patent airway, 2) adequate ventilation, and 3) prevention of aspiration of vomitus. Generally, a patent airway can be provided using a cuffed, inflated endotracheal tube provided that the animal is comatose or anesthetized. If the animal is extremely weak, convulsing, or has absent postural and/or swallowing reflexes and begins to vomit prior to intubation, inversion of the animal so that the head is lower than the rest of the body may clear the pharynx. Aspiration of the respiratory tract may be necessary. In larger animals the head may be lowered and the anterior thorax elevated to accomplish the same objective, e.g., placing the animal on an incline. After clearing the pharynx, endotracheal intubation can then follow.

When forced ventilation is needed for a prolonged period of time, ventilation with moistened room air is usually preferred over oxygen. Mechanical or manual forced ventilation may be necessary for poisoned animals suffering from paralysis, severe CNS depression or, rarely, when deep anesthesia is necessary to control convulsions. Assistance of ventilation is also the preferred method of correcting respiratory acidosis. In cases of profound anemia and/or hemorrhage, such as may occur in anticoagulant rodenticide poisoning or hypoxia resulting from various causes, minimal handling and oxygen cages may be of temporary benefit.

b) Maintenance of Cardiovascular Function

Provision of adequate respiratory ventilation, hydration, acid-base, and electrolyte balance are all necessary for normal cardiopulmonary function and oxygen exchange. Certain toxicants cause severe vomiting or diarrhea with resulting electrolyte and fluid imbalances. Ingestion of excessive quantities of drugs, especially diuretics can lead to extreme electrolyte alteration. Furthermore certain toxicants or toxic metabolites, such as oxalic acid, may bind calcium sufficiently to result in a hypocalcemic state. Thus, when cardiovascular dysfunction is associated with a toxic insult, correction of imbalances of calcium, sodium, potassium and acid-base status may result in restoration of normal function. Blood samples for electrolyte, blood glucose, and serum chemistry determinations should be collected before initiating fluid therapy. ECGs may be monitored and appropriate measures taken to reestablish homeostasis.

Fluid Therapy

Clinical guides to the assessment of fluid balance include features of serious flow volume overload (e.g., pulmonary edema) and volume contraction (e.g., skin turgor). If shock or hypotension occurs, balanced electrolyte solutions (e.g., lactated Ringer's solution) or normal saline are often indicated. Central venous pressure (normal for canine = 0 - 5 cm H_2O), urinary output, and body weight measurements may be monitored to avoid fluid overload and help adjust flow rate.

Estimation of Volume Deficit	
Percent Dehydration	**Clinical Signs**
5 - 6	Loss skin turgor, dry mouth, depression, oliguria, hypotension, shock
8	
> 10	

Remember that dehydration alone can influence various clinical pathology findings, e.g., increased PCV, increased BUN (prerenal azotemia), and elevated total protein. An adequate quantity of fluids must be supplied to replace deficits from previous losses. In addition, daily maintenance fluid requirements and on-going fluid loss (e.g., vomiting, diarrhea, polyuria) must be taken into account. In diarrhea, loss of sodium, potassium, magnesium, calcium, and bicarbonate can be expected. Ions lost through vomiting include chloride, sodium, and potassium.

Complications of Fluid Therapy

- Never give hypotonic or hypertonic fluids by any route other than intravenous.
- Complications associated with intravenous fluid therapy include:
  - overload (pulmonary edema, medullary washout),
  - Thrombophlebitis and endocarditis,
  - Pyrogenic reactions,
  - Air embolism,
  - Exsanguination (must be considered in coagulopathies, e.g., anticoagulants), and
  - Extravasation of fluids.

There is no single fluid that will fulfill the fluid requirements of all patients. A general guideline for maintenance fluid requirements is 50 - 80 ml/kg/day. Specific fluid guidelines are beyond the scope of this review; however, in the following conditions, appropriate fluid therapy includes:

Toxicant	Fluid
Hypercalcemia secondary to cholecalciferol ingestion	0.9% saline
Lactic acidosis, e.g., secondary to salicylate ingestion, or shock from any toxicosis	Saline and dextrose with bicarbonate; later after acidosis controlled, lactated Ringer's solution.
Ethylene glycol toxicosis	Saline initially, then lactated Ringer's solution alternated with 5% dextrose; bicarbonate may be added according to need
Conditions causing hemoglobinuria and myoglobinuria	Fluid therapy (saline) with added bicarbonate to lessen the likelihood of precipitation of hemoglobin or myoglobin in renal tubules

Blood Transfusion Therapy:

1. Calculation of blood replacement volume:

ml of Donor Blood in Anticoagulant needed

$$\text{body weight (kg)} \times C \times \frac{\text{PCV desired} - \text{PCV recipient}}{\text{PCV donor}}$$

where C is a constant depending upon the species involved. C = 90 (dog), 70 (cat). In larger animals, a general guide of 10 - 20 ml/kg could be used for clinically anemic animals.

2. Indications:

- PCV < 12 - 20%, depends upon history and clinical signs.
- Restoration of oxygen-carrying capacity.
- Hypovolemia, anemia, dyspnea.
- Fresh whole blood or plasma therapy used for volume restoration and coagulation factor replacement. Remember transfused platelets have short half-lives in the body.

3. Contraindications:

- Immune-mediated hemolysis.
- Blood group incompatibility.

Species	Major Blood Group	Minor (involved with most transfusion reactions)
Cat	A (73%)	B (23%), AB (1%)
Dog	F, C (98%)	A (40%), Tr (45%), other (see note below)
Horse	Multiple	Aa
Cow	Multiple	-

Note - Dog blood group current nomenclature "dog erythrocyte antigen" group (DEA), for example, A = DEA 8, Tr = DEA 7.

In many species (e.g., horse, cow, dog, cat), it is generally safe to administer transfusions to a recipient which has not received blood or blood components previously.

4. Transfusion reactions:

- Clinical signs of transfusion reactions include urticaria (most frequent), fever, hemolysis with hematuria, and anaphylaxis (arrhythmias, hypotension, cardiopulmonary arrest).
- Resultant renal failure secondary to hemolysis can occur.
- Hemolysis-May be acute or delayed.
- Acute hemolytic crisis within minutes-tremors, vomiting, urinary and fecal incontinence, transient fever, and prostration. More severe signs-dyspnea, paraparesis, and convulsions. DIC and shock, death possible.
- If see signs of reactions-stop transfusion and administer IV fluids. Check urine for hemoglobin/blood hemolysis.
- Most dogs recover in 12 - 24 hours.
- Circulatory overload; vomiting, cough, pulmonary edema may occur.
- Hypocalcemia due to blood containing sodium citrate. Other signs of citrate toxicosis include muscle fasciculations, arrhythmias, and collapse.
- Metabolic alkalosis from citrate that has been metabolized in stored blood to bicarbonate??
- Hyperkalemia-Stored (aged) blood has a high percentage of hemolyzed erythrocytes which results in the release of potassium.
- Small amounts (1 - 5% of total volume to be administered) should be given, then the animal should be observed closely for 10 - 15 minutes for anaphylactic reactions.
- Whole blood is given if red blood cell mass or platelets (use fresh plasma or fresh whole blood) are required.

For specific indications of diuresis, please see page A43.

Acid Base Disturbances

In the poisoned patient, acid base homeostasis may be disrupted by a variety of mechanisms. Acid base balance may be disrupted because: **1**) the toxicant or its metabolites have acidic or basic character; **2**) the agent causes seizures or other forms of profound exertion; **3**) the agent causes circulatory impairment of peripheral tissues (usually secondary to shock); **4**) the agent causes respiratory dysfunction; **5**) the agent causes vomiting or diarrhea; and/or **6**) the treatment (e.g., diuretics) causes electrolyte imbalance. Acidosis is the most commonly encountered acid base disturbance. Metabolic acidosis develops from a loss of extracellular bicarbonate (e.g., diarrhea), gain of hydrogen ion and decrease in bicarbonate concentration (e.g., aspirin ingestion), or from dilution of extracellular bicarbonate. Further classification of a metabolic acidosis into 2 general categories, based on the presence or absence of an elevated anion gap, may contribute to a diagnosis. For example, a partial list of toxicants resulting in an elevated anion gap includes ethylene glycol, methanol, and salicylates. Clinical signs of metabolic acidosis include tachypnea, vomiting, depression, and arrhythmias.

To correct metabolic acidosis (decrease in serum bicarbonate generally less than 18 - 22 mEq/L), fluids with added sodium bicarbonate (1 - 3 mEq/kg administered in fluids over 1 - 3 hours: an 8.4% solution sodium bicarbonate = 1 mEq/ml) are used. This is important with toxicosis due to ethylene glycol, metaldehyde, and aspirin among other agents. Blood gases and blood and urine pH are monitored to assess the need for and the success of bicarbonate therapy. Rapid alterations in pH with bolus dosages of alkalinizing agents must be avoided. Too rapid an administration of bicarbonate has been associated with cardiac arrest, hypotension, CSF acidosis, hyperosmolality, and vomiting. Other alkalinizing agents that have been investigated include sodium lactate, sodium acetate, and trihydromethyl aminomethane (THAM).

Metabolic **alkalosis** (sodium bicarbonate greater than 27 mEq/L) may be due to retention of excessive bicarbonate or loss of hydrogen (e.g., vomiting). Due to the resulting hydrogen ion gradient, intracellular hydrogen ions are exchanged for extracellular sodium and potassium resulting in hypokalemia. The resulting alkalemia depresses the central respiratory center and chemoreceptors resulting in hypoventilation and hypercapnia (respiratory compensation). Causes of metabolic alkalosis include diuretics, hypercalcemia, blood transfusions (remember stored whole blood is high in citrate which is converted to bicarbonate). Clinical signs of metabolic alkalosis include arrhythmia, increased neuromuscular irritability (e.g., tetany). To correct alkalosis, which is rarely a problem, fluid therapy (0.9% NaCl) with potassium chloride supplementation is generally effective. Ammonium chloride (200 mg/kg/day, divided dose) may be given orally.

Cardiac Arrhythmias - Treatment for cardiac arrhythmias may be required in some toxicoses. An arrhythmia is an abnormality in the rate, origin, or regularity of myocardial depolarization or other disturbance in impulse conduction. The clinical effects of an **arrhythmia may result from**: **1**) changes in the heart rate, **2**) loss of synchrony in atrial and ventricular contractions, **3**) heartbeat irregularity, **4**) changes in ventricular contractility. Clinical signs in an animal with an arrhythmia may include depression, weakness, ataxia, dyspnea, exercise intolerance, syncope, seizures, and/or death. Arrhythmias may also be suspected on the basis of physical exam findings including jugular pulse (may be normal in some cases), pulse deficits, and auscultable changes in heart sounds.

Methods available for the termination of arrhythmias include: **1**) physiological maneuvers (e.g., ocular pressure with some atrial tachycardias, temporary AV block); **2**) correction of acid base, electrolyte, or fluid disorder; **3**) oxygen therapy; **4**) antiarrhythmic drug therapy; and **5**) other supportive therapy. **Remember**, in many cases, correcting an underlying disorder may "cure" an arrhythmia without the use of antiarrhythmic drugs. When used, antiarrhythmic therapy should be specific for the type of arrhythmia present and the species involved.

Antiarrhythmic drugs are classified into 4 major categories based upon the drug's mechanism of action. Class I drugs interfere with fast current sodium channels and include quinidine, procainamide, and lidocaine. Class II drugs are ß-adrenoreceptor blockers and include propranolol and metoprolol. Class III drugs (e.g., bretylium) prolong the duration of the action potential. Class IV drugs are calcium-channel blockers; the prototype drug of this class being verapamil. Class I drugs have been subdivided into 3 subclassifications. Class IA drugs (e.g., quinidine, procainamide) have a moderate effect on conduction velocity and prolong repolarization. Class IB drugs (e.g., lidocaine, phenytoin) have mild effects on conduction velocity and shorten repolarization. Class IC drugs (e.g., encainide, lorcainide) markedly depress conduction velocity but have little or no effect on repolarization.

Horses - Anticholinergic agents including atropine or glycopyrrolate are used to treat bradyarrhythmias in horses. Ventricular rates less than 20 - 25 bpm should be treated. Remember that intestinal motility can be depressed (up to 9 hours after a single injection of atropine) following use of these agents. Doses (IV) of atropine (0.02 mg/kg) and glycopyrrolate (0.005 mg/kg) have been recommended for treatment of serious bradycardia due to increased parasympathetic tone (e.g., organophosphorus insecticide toxicosis). The best course of action is to administer atropine (only when needed) in fluids IV while frequently auscultating the abdomen in order to avoid induction of stasis. Side effects of atropine administration include diminished respiratory, salivary, and GI secretions, increased respiratory dead space, **colic**, and death.

In the horse, cardiac arrhythmias are treated with quinidine, procainamide, and propranolol. Quinidine is the most frequently used drug for the following types of arrhythmias: ventricular tachycardia, ventricular premature depolarization, atrial flutter, and atrial premature depolarization. Quinidine prolongs the QRS and QT intervals at therapeutic concentrations. The recommended dose of quinidine in the horse is 0.5 mg/kg IV every 10 minutes until 4.0 - 6.0 mg/kg total or 20 mg/kg oral every 2 hours until 60 - 80 g total. Large or toxic doses of quinidine can prolong the PR interval as well. Side effects of quinidine therapy in the horse include **pharyngeal swelling**, hypotension, depression, diarrhea, nervousness, and anorexia. Horses receiving large dosages may experience laminitis, tachypnea, and tachycardia. Sodium bicarbonate at 0.5 - 1.0 mEq/kg IV may be used to reverse some signs of quinidine toxicity.

Contraindications for quinidine therapy include shock, congestive heart failure, digoxin toxicity, cardiomyopathy, and bundle branch blocks. Treatment of sinus tachycardia is with propranolol.

A **partial list** of possible agents which could cause life-threatening arrhythmias in the horse include organophosphorous/carbamate insecticides, Japanese Yew, *Oleander* sp., Foxglove (*Digitalis*), digitalis, digoxin, and *Rhododendron*, among others. Note: calcium administration is contraindicated for digitalis compounds and the toxins present in *Rhododendron*.

Remember in the case of the horse, **autonomic-induced arrhythmias** may be due to excessive vagal stimulation and **may be normal** in the healthy horse. Using exercise as a means of diagnosis of arrhythmias (physiologic arrhythmias disappear when the heart rate is elevated) would be **dangerous** in the potentially poisoned equine.

Canine/Feline - Before attempting treatment of a cardiac arrhythmia, it is important to establish the possible agent involved and determine whether the animal is on any medication, especially digitalis. Remember that digitalis can cause almost all known arrhythmias. Treatment of an underlying cause of an arrhythmia (e.g., metabolic acidosis) may eliminate the arrhythmia or facilitate its therapy.

On a practical basis, antiarrhythmic agents can be divided into drugs for tachyarrhythmias or drugs for bradyarrhythmias. Some of the more common cardiac arrhythmias which may be expected in toxicoses include:

- Sinus bradycardia - Regular sinus rhythm with a heart rate less than 60 - 70 bpm in dog and less than 160 bpm in cat. If clinical signs, e.g., syncope or weakness, are associated with the arrhythmia, treatment should be considered. Parenteral atropine (0.01 - 0.2 mg/kg IV, IM) or glycopyrrolate (0.005 - 0.01 mg/kg IV, IM) would be initial antiarrhythmics of choice. Potential agents which may result in sinus bradycardia include organophosphorus/ carbamate insecticides, β-blockers, calcium channel blockers, digitalis, and phenothiazines.

- Sinus arrest (SA node does not produce conduction impulse) or sinoatrial block (conduction disturbance from SA node) when asymptomatic does not require therapy. These conduction blocks can result from propranolol or digoxin toxicity.
- AV blocks - Second-degree AV block (intermittent AV blockade) and third-degree AV block (no AV conduction) can also be caused by digitalis toxicity. Third-degree AV blocks generally require artificial pacing. Second-degree AV blocks can be treated with atropine, dopamine (3 - 5 mg/kg/minute), or isoproterenol (1 mg in 250 ml D5W drip slowly at .01 mg/kg/minute to effect).
- Atrial standstill is a potentially life-threatening arrhythmia and can be associated with hyperkalemia. **Hyperkalemic states** can be the result of increased exogenous K^+ load (e.g., excess KCl, blood transfusions), decreased renal excretion of potassium (e.g., toxicosis associated with potassium sparing diuretics, lithium, captopril, nonsteroidal anti-inflammatory drugs), and cellular shifts (e.g., due to digoxin, amphetamines, and 2^{o} rhabdomyolysis). If hyperkalemia is suspected (e.g., spiked T waves), the following therapies designed to shift potassium intracellularly may be of value: saline therapy, sodium bicarbonate (1 - 2 mEq/kg), or regular insulin (0.5 - 1.0 unit/kg) with dextrose (2 gm dextrose/unit insulin).
- Atrial tachycardia: originates from an atrial focus other than the SA node, arrhythmia may be secondary to digitalis toxicosis. Causes weakness, hypotension, and syncope. Vagal maneuver (e.g., ocular pressure) can terminate atrial tachycardia.
- Atrial flutter (rates ≥ 300 bpm) and supraventricular tachycardia or atrial fibrillation may also occur but are rarely observed in toxicosis.
- Ventricular premature complexes (VPCs) arise from ventricular ectopic foci and are commonly associated with a pulse deficit. Indications for treatment include: **a**) high rates 20 - 30 bpm, **b**) runs of VPCs, **c**) multiform QRS complexes, **d**) R on T phenomenon, and **e**) clinical signs, e.g., syncope, dyspnea, weakness. **VPCs rarely require therapy in the cat**, and in this species, propranolol (0.04 - 0.06 mg/kg slowly IV) or the more β_1 selective blocker, metoprolol would be indicated. **In the dog**, VPCs are commonly treated with lidocaine hydrochloride (**without** epinephrine, 2 - 4 mg/kg IV slowly to maximum 8 mg/kg, constant IV rate infusion 25 - 75 mg/kg/minute) or procainamide (6 - 8 mg/kg IV over 5 minutes, constant rate infusion 25 - 40 mg/kg/minute). Phenytoin has been recommended for digitalis-induced VPCs (30 - 35 mg/kg oral TID). A beta blocker may also be of value in conjunction with phenytoin and atropine for digitalis poisoning.
- Ventricular Tachycardia - May result in syncope, seizures, hypotension, etc. Antiarrhythmic therapy is generally warranted in most animals with ventricular tachycardia unless an underlying cause (e.g., electrolyte imbalance) can be identified and corrected. Lidocaine hydrochloride **without** epinephrine (2 - 3 mg/kg IV slowly) is the primary antiarrhythmic of choice **in dogs**. Constant infusion therapy may be required. Nonresponsive tachyarrhythmias, may require additional antiarrhythmic therapy, e.g., procainamide. When these fail, a β-blocker such as metoprolol may be of value.

Side Effects

As in all classes of therapeutic agents, antiarrhythmics have associated potential adverse side effects.
Phenytoin should not be administered to cats since small oral or IM doses have resulted in clinical toxicity, primarily manifested by hepatotoxicity.
Lidocaine is potentially neurotoxic in the cat and may cause tremors and convulsions, in addition to cardiac conduction disturbances, bradyarrhythmias, hypotension, and sinus arrest. Convulsions have been reported in the horse following administration of an IV bolus of lidocaine. **Note**: in the treatment of cardiac arrhythmias, lidocaine **without** epinephrine should be administered.
Digitalis glycosides can be used for the treatment of congestive heart failure and certain cardiac arrhythmias (e.g., supraventricular premature complexes, atrial flutter/fibrillation, supraventricular tachycardia). Signs of digitalis intoxication include increased P-R interval, AV block, prolonged QRS, and arrhythmias. Clinical signs of digitalis intoxication in the horse include anorexia, depression, and diarrhea. In addition to these signs, small animals may commonly vomit.
Untoward side effects of propranolol therapy include decreased contractility, bronchoconstriction, and bradycardia. Potential contraindications to ß-blocking drug use include: obstructive airway disease, congestive heart failure, bradycardia, hypoglycemia, and impaired AV conduction.

Note - These notes are not intended to be all inclusive and the reader is directed towards more comprehensive therapy reviews.

c. Control CNS Stimulation

Convulsions - Whenever possible, seizure treatment should be directed at the primary disease if it can be recognized. Seizures may be classified as partial or generalized. Generalized (grand mal) seizures are the most common form of convulsions in animals. Clinical signs include combinations of visceral (e.g., salivation, urination, defecation) and somatic (e.g., paddling, clonic limb activity) motor activity in addition to behavioral derangements.

Many cases, in which seizures occur as a result of a toxicosis, will require treatment for status epilepticus or repeated seizure episodes. The treatment of status epilepticus must be considered a **medical emergency** due to potential adverse sequelae (e.g., hypoxia, acidosis, etc.) if untreated.

Small Animals - Diazepam (Valium ®) (0.5 mg/kg IV or IM doses may be repeated every 10 minutes for 3 doses) may be used to control seizures from a wide variety of etiologies and therefore serves as a desirable choice for management of an animal (especially a dog) in convulsions, in which the causation is unclear. When diazepam fails, generally phenobarbital (6 mg/kg IV to effect) is tried next. If seizures persist, pentobarbital (slowly to effect) is usually used. Methocarbamol (Robaxin ®) (44 - 200 mg/kg IV start with low dose and give to effect) may be given when indicated for skeletal muscle relaxation IV. Injectable methocarbamol (Robaxin ®) contains a polyethylene glycol vehicle which may be contraindicated in animals with impaired renal function. Adverse reactions in dogs and cats include vomiting, hypersalivation, weakness, and ataxia.

Glycerol guaiacolate (Guailaxin ®) has been used to allow animals to relax enough to induce vomiting, but this application is controversial. Guaifenesin will also relax pharyngeal and laryngeal muscles and an animal may suffer loss of control of its airway. A dark quiet room with very frequent or constant monitoring is very important.

Hyperactivity

CNS stimulation from excessive exposure to amphetamines, or to some hallucinogens, such as LSD and phencyclidine have been treated with phenothiazine tranquilizers, but this therapy was not reliable enough to be widely accepted. As a rule, the phenothiazine tranquilizers are best avoided as they may aggravate CNS depression and in other cases be epileptogenic. If tranquilization is required (e.g., self-trauma), diazepam (2.5 - 10 mg IV PO to effect) should be considered.

d. Control CNS Depression

Remember that the presence of a toxicant does not necessarily account for an animal's neurological status. For example, some agents (e.g., barbiturates) may cause profound hypotension with resultant cerebral hypoxia in addition to their direct depressant effects. In addition, head trauma may result secondarily from the effects of a toxicant (e.g., falls, etc.). Repeated complete neurological examination of severely depressed or comatose animals is warranted to monitor status as well as response to therapy.

The use of **analeptics** is at best debatable since it is difficult to stabilize the animal receiving these drugs. Convulsions and rebound depression following withdrawal are undesirable side effects associated with older preparations. Clearly the best and only worthwhile respiratory stimulant is doxapram (Dopram-V®). This compound exerts its effect via stimulation of peripheral carotid chemoreceptors. The dosage of Dopram-V® is 1 - 10 mg/kg IV. Doxapram may be repeated in 15 - 20 minutes if needed. Some human protocols additionally employ a slow drip of doxapram HCL. Doxapram is compatible with 5% dextrose or normal saline but not with alkaline solutions. In doses greater than those used to stimulate respiration, CNS stimulation by doxapram may result in seizures. The drug is considered to have a narrow margin of safety. Other adverse effects (reported in humans) include hypertension, arrhythmias, and dyspnea. After the period of stimulation, deepening of the comatose state usually reoccurs, but sometimes not to the original extent. Sometimes judicious stimulation may increase the activity of the CNS to the point that the restoration of vital function may secondarily produce a further awakening effect.

The use of naloxone is recommended for the treatment of exogenous opiates (e.g., morphine, codeine). Naloxone has replaced levallorphan and nalorphine in clinical treatment because it lacks agonist activity. Naloxone's duration of action is short (45 - 90 minutes), and in the treatment of opiate-induced coma, higher doses may be required. Naloxone is administered in dogs at .04 mg/kg IV, IM, or SC and is repeated as needed. Experimental and clinical data in rabbits and humans indicate that naloxone is efficacious when administered by the endotracheal route. A nonspecific arousal effect has been attributed to naloxone with reports in human clinical cases of the reversal of nonopiate central nervous system depression from barbiturates and benzodiazepines.

Flumazenil has been shown to be an effective treatment for CNS depression associated with benzodiazepine overdose in dogs. The drug is a specific benzodiazepine antagonist with a very wide therapeutic index. The dose is based on an estimate of diazepam intake (1 mg flumazenil /25 mg diazepam) and is given intravenously. Duration of activity is approximately 2 hours. Re-dozing may be required in cases of severe toxicosis.

Physostigmine

Is an alkaloid extract of the Calabar bean. Its active constituent is an uncharged carbamate cholinesterase inhibitor. The use of physostigmine for its nonspecific arousal effect has been advocated in humans poisoned with tricyclic antidepressants, ivermectin, benzodiazepines, phenothiazines, barbiturates, and ketamine. It also is used for life threatening toxicosis from atropine and related compounds. The use of physostigmine has become associated with considerable controversy, however. Adverse effects associated with physostigmine include convulsions, cholinergic crisis (e.g., hypersalivation, bradycardia, dyspnea), variable levels of consciousness and possible death. Physostigmine is rapidly metabolized and requires repeated administration (every 30 - 60 minutes) to maintain its effects. Due to its clinical limitations and possible adverse side effects, its general use as an analeptic cannot be recommended.

e. Control Body Temperature

Hypothermia may occur during anesthesia, heavy sedation or coma. Body temperature may decrease below the calibration of a rectal thermometer during prolonged anesthesia. Such a condition may occur during the course of therapy for strychnine poisoning. Vital physiologic processes and the rate of metabolic degradation of poisons are depressed when body temperature is subnormal. Blankets and circulating warm water pads may be helpful in maintaining body temperature. If heat lamps are employed, be careful to avoid burning the animal. It is best to use these only at a distance to heat the environment rather than the animal directly. Animals with poor perfusion are more likely to be burned. Turn the animal often and check the temperature to avoid hyperthermia. Conventional heating pads can also cause burns and should be avoided.

Hyperthermia often occurs with persistent seizures. Hyperthermia is controlled with ice or cold baths. Concomitant dehydration may occur and should be controlled. Hyperthermia may also be a problem with toxicosis due to uncouplers of oxidative phosphorylation, e.g., disophenol (DNP), pentachlorophenol and dinitrophenol. With poisoning from these agents it is important to keep the animals calm and as cool as possible even before the onset of signs. Elevated body temperature from either exercise or ambient temperature tends to precipitate acute toxicosis. Antipyretic drugs are generally not indicated in toxicant induced hyperthermia.

5. Preventing Continued Absorption of the Toxicant

a. Dilution

The oral administration of water or milk is frequently recommended in the initial management of poisoning. This recommendation is based upon the potential for dilution of a toxicant with delayed or decreased gastrointestinal absorption. In several studies, large volumes of water apparently increased gastrointestinal absorption and decreased oral LD_{50} when a chemical was given concurrently with water. The administration of water or milk to facilitate dilution of a toxicant has therefore become controversial.

It is still generally recommended that dilution with water or milk may be useful, along with demulcents and gastrointestinal protectorants in the management of corrosive ingestions.

Corrosive Ingestions

Various sources of alkaline corrosives include lye (concentrated sodium hydroxide), drain cleaners, some electric dishwashing detergents, phosphate detergents, bleaches, and batteries. Alkaline batteries may cause intestinal necrosis if they become opened in the GI tract. Most liquid chlorine bleaches, dilute ammonia, and other weaker alkaline corrosives may result in burns but are less caustic to the esophagus. In general, alkaline corrosives are considered more damaging since their ingestion results in a liquefactive necrosis. Acids more commonly produce a coagulative necrosis which minimizes tissue penetration. Granular or solid lye more commonly adheres to mucous membranes, and their ingestion is associated with a higher incidence of pharyngeal and esophageal burns. Esophageal injury in the absence of mouth or pharyngeal burns can occur and may require careful esophagoscopy, barium swallows, or other radiologic evaluation for diagnosis.

The use of chemical neutralizing agents (e.g., vinegar, sodium bicarbonate) has been demonstrated to be associated with increased tissue damage and is contraindicated. Emetics are also contraindicated, and due to possible esophageal damage, gastric lavage is also unadvisable.

Dilution of orally ingested strong acids or alkalis or other irritating substances with milk or as a second choice water does not "prevent exposure" per se, but it may serve to prevent exposure to sufficient concentrations which may otherwise exert much more serious mucosal and/or submucosal corrosion. Administration of demulcents such as milk, egg white or kaolin-pectin preparations may be of further value in protecting the damaged mucosae. To be effective, the demulcent must be used very soon after exposure to the toxicant.

For further protection of the damaged mucosa of the digestive tract, the use of the anti-ulcer medication sucralfate may be tried. Sucralfate is available through human pharmacies and is an anti-ulcer agent comprised of an anionic, sulfated disaccharide. The drug inhibits pepsin and binds bile acids. It also forms a polymer when in contact with water molecules and hydrochloric acid, as in the stomach. The paste-like polymer formed by sucralfate is believed to adhere to the gastroduodenal mucosa, especially in ulcerated areas where it locally buffers acidity. Sucralfate has been shown to bind to acute gastric erosions caused by other agents such as aspirin. The barrier formed by the sucralfate therefore tends to protect the ulcer from acid, bile and pepsin so that healing can occur.

Only 5% of administered sucralfate is absorbed from the gastrointestinal tract so that the remainder is available to act at the digestive system mucosae. Sucralfate is very low in toxicity. Animals have tolerated doses of 12 g/kg. Sucralfate is dosed in the dog based upon extrapolated human dosage schedules.

The role of steroids in the prevention of esophageal strictures in animals that have experienced deep circumferential burns of the esophageal mucosa is unclear. Evidence from animal studies indicate the use of steroids may reduce stricture formation, and their use for 1 - 2 weeks post-ingestion may be warranted.

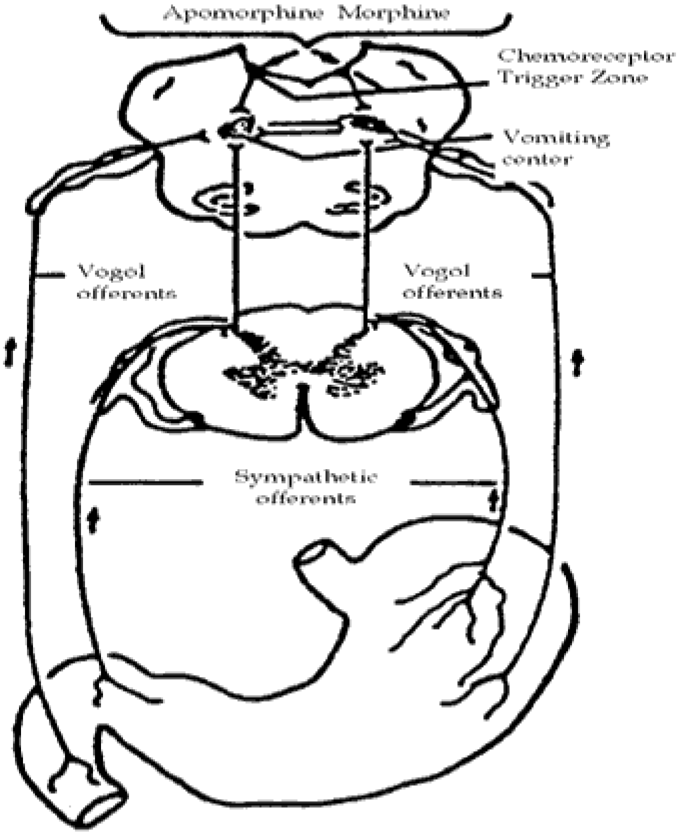
b. Removal of the Toxicant from the Gastrointestinal Tract

- A review of the physiology of emesis is helpful in understanding the pharmacology of emetics. There are five stimuli that induce emesis in animals. These are:

- direct stimulation of the central nervous system by foreign chemicals (xenobiotics) in the blood
- pharyngeal stimulation (transmitted via the glossopharyngeal nerve: cranial nerve IX)
- visceral irritation (transmitted via visceral afferent fibers in the sympathetic or vagal (X) nerves or the spinal cord)*
- vestibular (labyrinth) stimulation (accounts for motion sickness: transmitted via the acoustic nerve (VIII)
- stimulation from connections to the cerebral cortex (fear, pain, head injury, increased intracranial pressure, etc.).

*Visceral efferents of the stomach and upper intestinal tract are incorporated into the vagus (X) nerve. However, stimulation from irritation of the lower intestinal tract or urinary tract is carried to the brain via visceral efferents in the spinal cord.

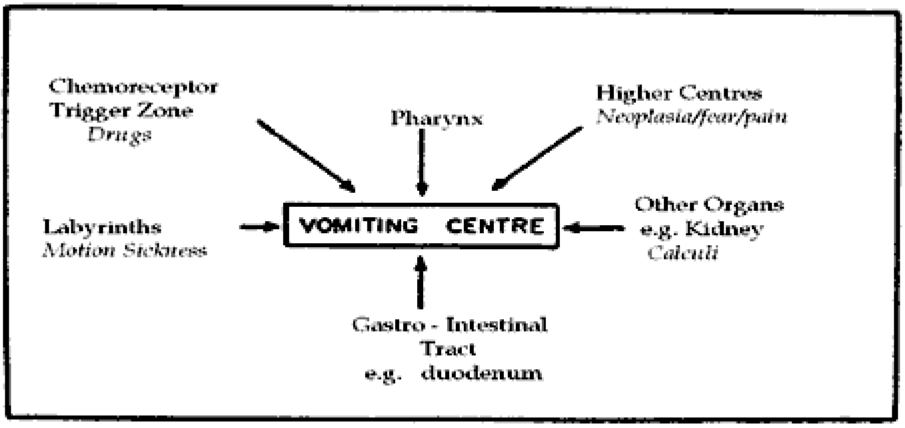
All of these stimuli cause input into the emetic center. The emetic (vomiting) center is an accumulation of nuclei in the reticular formation of the posterior medulla. The emetic center requires prolonged and continual stimulation by afferent input before the summation of these stimuli is sufficient to induce emesis. Temporal and spatial summation of input from the chemoreceptor trigger zone (CTZ), and the vagal, glossopharyngeal and other nerves occurs within the emetic center. This also appears to occur with information coming from the reticulospinal tract.



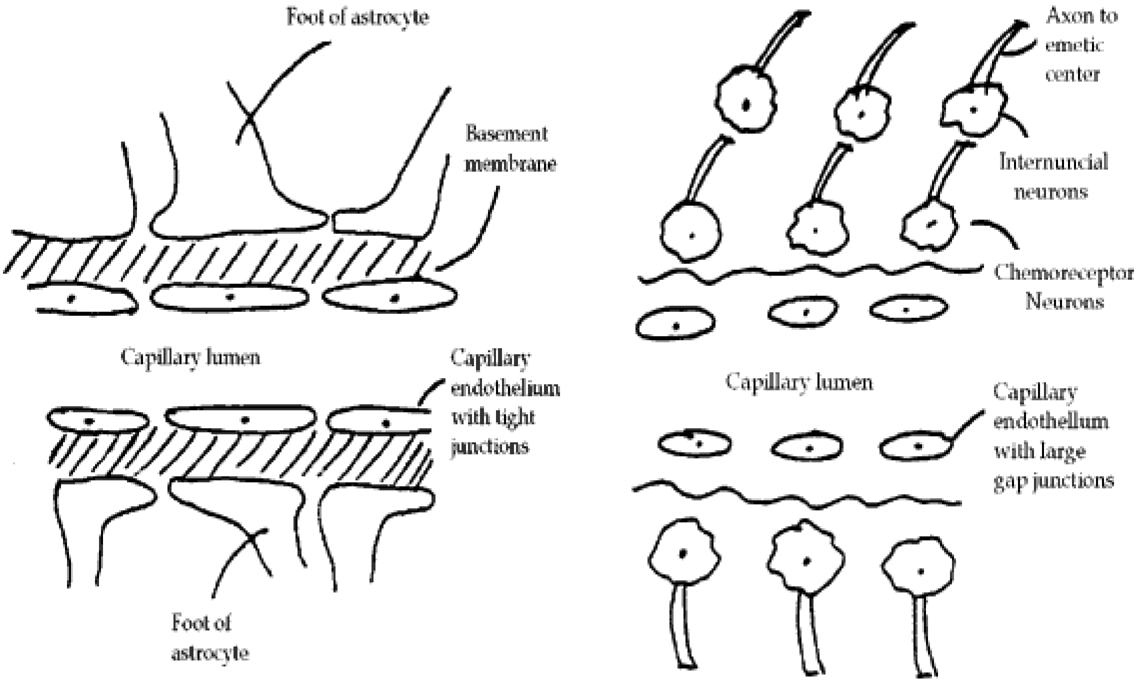
The Afferent Connections of the Vomiting Center

Chemoreceptive neurons (the CTZ) are located in the area postrema of the medulla. The unique structural arrangement of the capillary endothelium of this region in conjunction with these specialized neurons allows the area postrema to monitor the concentrations of xenobiotics and other chemicals in the blood. This function of the area postrema is made possible by the absence of the blood-brain barrier since the capillaries of this region have large gap junctions. Immediately adjacent to these "porous" capillaries are the chemoreceptive neurons which are stimulated when a threshold concentration of a xenobiotic is reached. The chemoreceptive neurons have direct internuncial connections with the emetic center.

Repeated stimulation of the vestibular organ may also cause emesis. Generally this requires a prolonged and rhythmic motion to which the animal is not accustomed, such as occurs during travelling. Vestibular input to the emetic center may rarely occur with inner ear dysfunction. These impulses are mediated indirectly through interconnecting internuncial neurons.



The Blood Brain Barrier vs. the Absence of the BBB in the Chemoreceptor Trigger Zone



Model of blood brain barrier. Most areas of the brain.

Model showing absence of BBB in CTZ located in the area postrema of the medulla.

Diagrammatic presentation of the transmitter mechanisms associated with chemoreceptor trigger zone.

The act of vomiting is a complex and highly coordinated process. This coordination occurs in the vomiting center. In the pre-emesis phase ptyalism is usually observed. This is rapidly followed by relaxation of the stomach musculature and dilation of the pyloric region of the stomach. At this point reverse peristalsis of the duodenum commences. Swallowing of air, then inspiration against a closed glottis creating a reduced pressure in the thorax is accompanied by an increase in abdominal pressure from respiratory movement (contraction) of the abdominal musculature. Contraction of the pylorus, relaxation of the body of the stomach, gastric reflux and esophageal collapse occur in cyclic repetitions. The gastric contents are forcefully expelled by contraction of the abdominal wall against a caudally moving diaphragm. The flattening of the diaphragm that results is reportedly responsible for opening the cardiac sphincter. During this process, the esophagus relaxes and the stomach expels its contents into the esophagus. Some workers indicate that the stomach actually invaginates into the esophagus. They report that, in dogs, the stomach may reach the level of the fifth rib. With sufficient stimulation, the vomiting process may be repeated every two to three minutes for several hours unless there is medical intervention.

Contraindications To the Use of Emetics

Emetics are **never** given to **rodents**, **rabbits**, **horses** or **ruminants**. Rodents are incapable of vomiting; rabbits and horses reportedly do not have a stomach wall strong enough to safely tolerate emesis; and safe and effective doses of emetics have not been defined in ruminants.

Neither emesis nor gastric lavage are recommended in cases where strong alkali, acid, or other highly corrosive materials have been ingested. The extreme contracture of the musculature during vomiting may be sufficient to rupture an already damaged esophagus or stomach leading to spillage of ingesta into the surrounding tissues with secondary mediastinitis or peritonitis.

The esophagus, unlike the rest of the digestive tract does not have a significant protective coating of mucus secreted by goblet cells and is quite susceptible to caustic and corrosive materials. The initial exposure of the esophagus to a corrosive agent may destroy the protective epithelium leaving the muscular layer exposed and thereby next in line to be damaged if the corrosive substance is brought back up. Constriction of fibrous tissue laid down during healing, may lead to stricture formation.

Emetics should not be given to animals that are hypoxic, dyspneic, seizuring, extremely weak, comatose, lacking normal pharyngeal reflexes, or suffering other marked neurologic impairments that could lead to aspiration pneumonia. Emetics should **not** be given to animals that already have vomited profusely or when they have vomited blood. Emetics are **never** given to sedated animals. Also, emetics **never** should be given to animals that have endotracheal or intragastric tubes in place. During seizures the gag reflex may be lost and vomiting may result in aspiration. Also, if the animal has ingested a CNS stimulant, further stimulation associated with vomiting may precipitate seizures. Thus, inducing emesis **often is contraindicated** following exposure to CNS stimulants.

Previous administration of drugs with anti-emetic activity will sometimes block the effects of emetics (see Table I). Individuals poisoned by noncorrosive substances, but not candidates for emesis, may often benefit from gastric or enterogastric lavage.

Hydrocarbon Controversy

The use of either emetics or lavage in cases of volatile hydrocarbon ingestion is controversial. Commonly ingested hydrocarbon products include gasoline, kerosene, paint thinner, solvents, turpentine, mineral spirits, lighter fluids, furniture polish, and insecticides. Aspiration of hydrocarbons has been attributed to inhalation of the hydrocarbons during emesis. Although, the irritating properties of gastrointestinally absorbed hydrocarbons that volatilize in the lungs appears to be essentially the same as those observed with aspiration pneumonia, only extremely large quantities of ingested hydrocarbons are likely to be associated with substantial pulmonary complications from absorption alone. Hydrocarbons with low viscosity have a greater aspiration risk than hydrocarbons with high viscosity. **The volume of the liquid ingested is less important than the viscosity in determining aspiration potential**. Gasoline, xylene, toluene, lighter fluid, and mineral seal oil all have low viscosity and are associated with a high risk of aspiration.

Clinical signs associated with hydrocarbon ingestion include cough, dyspnea, tachypnea, depression, bronchospasm, tremors, cardiac arrhythmias, seizures, and vomiting. Ingestion of chlorinated hydrocarbons, e.g., trichloroethanes, carbon tetrachloride, and methylene chloride is also associated with hepatotoxicity, and one of the metabolites of methylene chloride is carbon monoxide. Aromatic nitro and amino compounds (e.g., nitrobenzene, nitrophenol, nitroaniline) may cause methemoglobinemia in some species. The presence of coughing following ingestion should alert the clinician to potential aspiration. The presence or absence of coughing is not conclusive for aspiration having occurred.

Treatment of hydrocarbon ingestion is directed towards symptomatic and supportive therapy. It is important to keep in mind that pulmonary complications are the most common life-hreatening clinical problem. In general, petroleum distillates are poorly absorbed from the gastrointestinal tract. Thus, kerosene (given intragastrically at 22 ml/kg to dogs with transected esophagi) or charcoal lighter fluid (given intragastrically at 10 ml naphtha/kg to rats) did not cause significant illness or lesions. However, the potential pulmonary effects of other hydrocarbons after ingestion may be greater. For example, rats given turpentine (hydrocarbon comprised primarily of secondary and tertiary cyclic terpene alcohols = 80% terpenes) orally (at a dose of 5 ml total dose: animal weight not specified) developed pulmonary edema and hemorrhage.

The oral toxicity and aspiration hazard of most high-viscosity hydrocarbons (e.g., paraffin wax, tar, etc.) is so low that removal is seldom a concern. Some human clinical toxicologists have recommended the use of emetics if large (> 1 ml/kg) amounts of medium-range-viscosity (e.g., gasoline, kerosene, turpentine) hydrocarbons have been ingested. However, due to the apparently low risk of pulmonary problems from ingested hydrocarbons, emesis is no longer recommended by most toxicologists. Emesis is never recommended for the ingestion of low-viscosity (e.g., mineral seal oil, furniture polishes) hydrocarbons because of the increased risk of aspiration into the lungs.

Note - Mineral seal oil (a replacement for seal oil, derived from seals) has a great tendency to "creep" up the esophagus and be aspirated into the trachea.

Despite the general contraindication to the use of emetics in hydrocarbon ingestions therapeutic approach to hydrocarbon ingestion must always take into account the type of hydrocarbon ingested, the initial clinical presentation of the patient and amount. Emesis may still be recommended for minor amounts of hydrocarbons if they contain: camphor, potent pesticides, heavy metals, halogenated solvents, or especially toxic hydrocarbons such as benzene.

In human medicine, the incidence of aspiration pneumonia appears to be higher in cases treated with gastric lavage than when emesis is induced with syrup of ipecac. Other data indicates that aspiration occurs with initial ingestion and not with vomiting. At present, gastric lavage is generally not recommended for hydrocarbon ingestions.

The use of orally administered olive or mineral oil to increase the viscosity of ingested hydrocarbons is also controversial and cannot be recommended. Antibiotics may be required if secondary infection is superimposed on a chemical pneumonitis. Choice of antibiotics should be based upon culture and sensitivity results. Steroids may be associated with increased positive cultures, and therefore their administration is not recommended unless shock develops.

Chest x-rays should be obtained **initially** to evaluate the animal for aspiration pneumonia. Radiographic evidence of aspiration pneumonia may be delayed for 6 - 8 hours following aspiration, necessitating **serial** radiographs.

Indications for Emetics

The use of emetics in emergency treatment of poisoning is a matter requiring good clinical judgment. Various toxicants are absorbed at different rates and in different parts of the gastrointestinal tract. Small uncharged molecules (e.g., ethylene glycol) or charged acidic drugs (e.g., aspirin) which receive a proton in the highly acid environment of the stomach are often absorbed comparatively rapidly, directly through the gastric mucosa. Basic drugs (e.g., amphetamine) are charged in the stomach, and are therefore poorly absorbed in this location. It follows that to be maximally effective when dealing with compounds absorbed directly from the stomach, emesis must be used as rapidly after exposure as possible.

At times radiographs of the abdomen may reveal the location of sufficiently radiodense or radiolucent ingesta which may be of use when deciding whether to employ an emetic. Some drugs and toxicants delay gastric emptying. Therefore, **no strict rule of thumb applies to how long after ingestion an emetic may be of benefit.**

Emesis is generally more efficient than lavage in removing the offending material from the stomach. The response to emetic drugs varies but gastric emptying is generally effective in removal of 40 - 60% of the chyme from the stomach when vomiting successfully occurs. Pharyngeal stimulation is only rarely effective and when vomiting occurs only roughly 25% of the stomach content is removed. **Note**: Do not forget to freeze the initial vomitus for analytical confirmation.

The veterinarian must be concerned with the need for sufficient mass in the stomach to be propelled by the physical events that comprise retching and vomiting. This is especially important when an animal has not recently eaten food but has consumed a low volume, highly toxic poison. In such instances, when an emetic is to be given, feeding just before administration of the emetic is likely to be of some benefit. Fatty foods, which tend to enhance the absorption of lipid soluble agents, such as many organic pesticides and other toxicants should generally be avoided.

Table 1. Antiemetic Drugs that are Common Accidental Poisonings
Phenothiazine tranquilizers Marijuana Diazepam and other benzodiazepine compounds Barbiturates Antihistamines, especially those which act on the H_1 receptors Dimenhydrinate (Dramamine ®) Codeine Antidepressants Meprobamate

Specific Emetics:

Apomorphine - Apomorphine is the drug of choice in dogs, but despite attempts, a safe, effective dose has not been established for cats. Its mechanism of action is stimulation of dopaminergic receptors in the chemoreceptor trigger zone and perhaps stimulation of the emetic center itself. Apomorphine is sold in 6 mg tablets which are used to make a solution for administration via the conjunctival sac or IV.

Advantages of the use of apomorphine in dogs include:

- The vomiting response is fast and dependable. Following intramuscular administration, emesis occurs in an average of 4.5 minutes but, vomiting is occasionally prolonged. After intravenous administration, however, emesis is produced immediately and is of short duration (1 - 2 minutes) (therefore the intravenous route is preferred). Intraconjunctival use (crush part of a tablet in a syringe with a few drops of water-administer by drop into conjunctival sac) is convenient and usually effective but is somewhat less likely to be successful than intravenous use. However, the dosage can be partially regulated by washing the conjunctival sac free of unabsorbed apomorphine. In experimentally dosed dogs, the percent recovered of an orally administered dose of barium sulfate has been reported as 78% when apomorphine was given simultaneously with barium, 64% when given 30 minutes later, and 25% when given 60 minutes later.
- The emetic effect is usually temporary, particularly when the drug is given intravenously. Apomorphine and other morphine-like drugs also inhibit the firing of the emetic center. The aim of apomorphine therapy, therefore, is to excite the chemoreceptor trigger zone before the emetic center is inhibited. In both areas the effect is concentration dependent. Since the area postrema is devoid of histologic features of the blood-brain barrier, substances in blood will transport into the chemoreceptor trigger zone more rapidly than into the emetic center. However, if the apomorphine is absorbed slowly, as from oral administration, the concentration gradient between the chemoreceptor trigger zone and the emetic center may not be sufficient to result in the desired sequence of events.

Disadvantages of apomorphine include:

- It is not recommended for cats because safe and effective dosages have not been demonstrated and it would appear that the cat is much less sensitive to apomorphine-induced emesis than the dog. Also, reportedly apomorphine is not particularly effective in swine.
- Overdosage in dogs may result in CNS depression, respiratory depression or rarely in restlessness, excitement or even convulsions. Other side effects include protracted vomiting. CNS and respiratory depression may be reversible with the pure narcotic antagonist naloxone.
- It is unreliable when given by mouth.
- Apomorphine solutions must be made up fresh as they are unstable in light or air. If the solution is green the tablet has already partially decomposed and reliable emesis is no longer assured.
- Previously absorbed antiemetic drugs may prevent vomiting subsequent to apomorphine administration.

The dosage of apomorphine in dogs is IM-0.04 mg/kg and IV-0.03 mg/kg.
Note - different texts recommend 0.02 - 0.04 mg/kg; apomorphine has been experimentally evaluated at higher doses of 0.066 or 0.05 mg/kg). Apomorphine comes as a hypodermic tablet (6 mg) to be dissolved in sterile water prior to use. **Note**: One source (Booth and McDonald, 1982) indicated that pretreatment with naloxone IV, at a dose of 0.04 mg/kg, did not prevent apomorphine induced emesis in dogs. This reference goes on to suggest that potent antagonists of apomorphine include haloperidol, spiroperidol and pimozide; and states that these drugs possess "pure dopamine receptor blocking activity".

Morphine - As with apomorphine, morphine usually stimulates the chemoreceptive neurons before it depresses the emetic center. Therefore it has both emetic and antiemetic activity. Morphine, however, stimulates the chemoreceptor trigger zone at a site different from that stimulated by apomorphine. Morphine is used as an emetic in dogs but it is much less reliable than apomorphine. Also, one of the most readily available preparations contains atropine which is contraindicated due to delayed intestinal transit time which can result in increased toxicant absorption. Unlike the case of apomorphine, naloxone will block the emetic effect of morphine in the dog. Since Nalline® (nalorphine) and Lorphan® (levallorphan) have narcotic agonist action as well as antagonist action and thus may depress the central nervous system, the more "pure" narcotic antagonist naloxone, also called Narcan®, is preferred to counteract apomorphine-associated depression. The recommended dose of naloxone for dogs is 0.04 mg/kg IV, IM, or SQ.

Syrup of Ipecac - **Avoid** using the **fluid extract** of **ipecac** as it is highly toxic. Toxic effects of fluid extract of ipecac include diarrhea, cardiac arrhythmias, peripheral vascular collapse and death. The fluid extract is 14 times more concentrated than the syrup. Syrup of Ipecac U.S.P., the desired form, contains 2% alcohol and 7% ipecac in a glycerin vehicle. Ipecac is derived from the dried root of either *Cephaelis ipecacuanha* or *Cephaelis acuminata*, and its active principles are the alkaloids emetine and cephaeline. Of these alkaloids, cephaeline is the more toxic and causes more nausea and vomiting, whereas emetine is primarily cardiotoxic. It is available over-the-counter in 1 oz. bottles. Many persons with small children keep syrup of ipecac on hand. Ipecac acts by local irritation of the stomach and, when its active alkaloids are absorbed in adequate amounts, by stimulation of the hemoreceptor trigger zone of the medulla.

In dogs which were experimentally administered barium sulfate, ipecac syrup was 62%, 44%, and 30% effective in recovering the barium sulfate when administered immediately, 30 minutes, or 60 minutes, respectively, after barium ingestion. A decrease in the recovery rate of ingested material has also been demonstrated in dogs given sodium salicylate where a 30-minute delay in inducing vomiting resulted in a 44% recovery rate. This was in contrast to the observed recovery rate of 39% if vomiting was further delayed. Syrup of ipecac-induced emesis was superior to gastric lavage in recovering salicylate from the stomach of children in one study.

The **dose of syrup of ipecac for dogs is 1 - 2 ml/kg**. Only if the lower dose is used may the dose be repeated, and then only once. Note: Cats have been experimentally dosed with syrup of ipecac as either a 50% solution (diluted with water) or an undiluted solution. Doses **with the 50% solution** were 2.2 and 6.6 ml/kg (equivalent to 1.1 and 3.3 ml/kg if undiluted) and vomiting was reliable at all the doses. At the lower doses, however, vomiting was delayed. After the lowest dose (1.1 ml/kg), the mean time to emesis was unacceptably long (40-63 minutes: mean of 52 minutes). At the intermediate dose (3.3 ml/kg), vomiting occurred in 5 out of 5 cats after a latent period of from 11 to 34 minutes: mean of 23 minutes). Emesis did occur faster with the highest (6.6 ml/kg of undiluted syrup of ipecac) dose (range of 9 - 17 minutes, mean of 11 minutes], but the cats displayed a reduction in activity and salivation which persisted for several hours. In spite of mentioning these effects, the author stated that "no signs of depression" were seen. The **dose of syrup of ipecac, presently being recommended for cats, is 3.3 ml/kg of body weight**. In instances in which otherwise healthy cats have ingested potentially lethal doses of a toxicant, the use of the higher dose (6.6 ml/kg) of syrup of ipecac seems well justified, unless activated charcoal or another effective adsorbent can be relied upon to effectively bind the toxicant in question.

The preferred way of administering syrup of ipecac to cats is to dilute it 50/50 in water so that a total volume of 6.6 ml/kg (3.3 ml/kg of undiluted syrup of ipecac) can be administered via a No. 12 French rubber urethral catheter using a mouth gag. Cats may object to oral administration and the dilution in water also facilitates passage through a nasogastric or stomach tube. The dose is administered once.

Even syrup of ipecac well beyond the expiration date (at least up to a few years) may be used. Activated charcoal adsorbs and therefore should not be used concurrently with ipecac at least until after emesis or apparent failure of the emetic.

As mentioned above, when administering any emetic, the veterinarian must realize that "you can't squeeze an empty balloon". In other words, stomach contents must be of sufficient volume to allow vomiting, but when administering an emetic that relies upon gastric irritation or absorption, such as syrup of ipecac, too much dilution may decrease gastric irritation, reduce the rate of absorption, and therefore diminish the efficacy of induction of vomiting. Thus, water at 5 ml/kg is indicated immediately after emetic administration if the animal has a nearly empty stomach. The administration of milk with syrup of ipecac has been associated with a delay in the onset of emesis.

It has been postulated that the ingestion of antiemetic compounds (e.g., phenothiazines, anticholinergics, and tricyclic antidepressants) would produce a diminished response to emesis induced by syrup of ipecac. In humans, however, the time to onset of emesis as well as percentage responding to syrup of ipecac was not diminished in patients which had ingested an antiemetic. Use of an emetic would not be recommended for agents like benzodiazepines and tricyclic antidepressants due to their rapid onset and risk of aspiration. The major concern about ipecac toxicity is that of cardiotoxicity. In humans receiving emetine therapy, reversible EKG abnormalities were observed. Cardiotoxicity is not anticipated from the recommended doses of **ipecac syrup**.

Hydrogen peroxide - H_2O_2 (3%) is easily administered orally especially using a syringe or plastic squeeze bottle inserted between the teeth. It may be effective alone or may be used with apomorphine on the infrequent occasions when the former is initially ineffective. The dose of 3% hydrogen peroxide is 5 to 15 ml per 10 pounds body weight, and this can be repeated up to two times if emesis does not occur within five to ten minutes after dosing. Also, 3% H_2O_2 has been suggested for use as an emetic in swine. The dose may be given via the external nares. Concentrated hydrogen peroxide, such as the kind used in hair bleach should not be confused with 3% solutions and should not be given to animals.

Xylazine - Xylazine is somewhat effective as an emetic in cats. The pharmacologic effects are not reversible with a narcotic antagonist. Xylazine may aggravate respiratory depression and cause parasympathetic slowing of the heart. The dosage of xylazine to induce emesis in cats is 1.1 mg/kg (0.5 mg/lb) IM or SQ. The α-2 adrenergic blocking agent yohimbine has been used in a number of species to reverse the central nervous system depression that results from xylazine's actions on α-2 adrenergic receptors. A dosage of 0.1 mg/kg IV yohimbine in dogs and cats reverses CNS depressant, bradycardic, and hypotensive effects of xylazine in dogs. At dosages of yohimbine greater than 0.5 mg/kg, excitement, tachycardia, and hypertension may develop.

Yohimbine has also been reported to shorten ketamine-induced anesthesia in cats through an unknown mechanism.

Liquid Dish Detergent and Liquid Emetic Agent (LEA) - LEA is an experimental detergent-based, strawberry flavored oral emetic, which is rapid and effective. LEA consists of sodium tripolyphosphate (12%), tetrapotassium pyrophosphate (8%), sodium saccharin (2.5%), and a strawberry flavoring. The drug induces vomiting even when chlorpromazine has been administered, suggesting a local effect by LEA. Because of economic and legal concerns, LEA is not likely to be made available commercially. Orally administered liquid dish detergent is also somewhat effective as an emetic as demonstrated in experimental trials in children in which doses of 30 ml and greater were used and may be effective when ipecac or hydrogen peroxide is not available. When tried in a small number of cats, liquid dish detergent was not particularly effective.

Copper Sulfate - Copper sulfate is an emetic exerting its effect by direct gastric irritation. The agent must be made up fresh each time just prior to administration. In the past, copper sulfate was used as an emetic for children in a dose of 150 - 250 mg dissolved in 30-60 ml of water. The emetic action of copper sulfate was reliable (93 of 100 children vomited). The time to induce vomiting ranged from 0 - 40 minutes with a mean of 6.9 minutes. Although ceruloplasmin and serum copper levels increased, no obvious hemolysis or liver dysfunction was apparent. However, increased urinary excretion of copper, proteinuria, and renal and hepatic damage have been reported. The potential for copper poisoning has precluded widespread application of copper sulfate as an emetic.
Copper sulfate and zinc sulfate induce emesis in dogs even after surgical ablation of the chemoreceptor trigger zone. The gastric reflex afferent nerves, which stimulate the vomiting center and are responsible for copper sulfate induced emesis, are not completely blocked by sectioning the vagus nerves. As little as 40 mg of copper sulfate given orally will induce emesis in the dog.

Lobeline - Lobeline sulfate is an effective emetic drug that has been evaluated in dogs at a dose of 10 mg/kg SQ. Unfortunately at 12 mg/kg, a very slightly higher dose, dogs developed hyperactivity and convulsions. The margin of safety is obviously far too low to recommend.

Dry Powdered Mustard - When added to warm water, one of the glycosides of mustard is hydrolyzed to liberate the volatile oil (allyl isothiocyanate). Black mustard (from *Brassica nigra*) is richer in the volatile oil than is the yellow variety. All prepared mustards are ineffective as emetics. The dose of dry powdered mustard is "1 to 4 teaspoons in 1 cup of warm water". It is not highly recommended for it is largely ineffective. The mechanism of action is reported to be gastric irritation.

Prostaglandin F2-α - Prostaglandin F2-α has been evaluated in a single study as an agent to stimulate vomiting and defecation in the dog. At a dose of 0.111 mg/kg (presumably SQ, route not stated in the paper), defecation consistently occurred without vomiting. At a dose of 0.444 or greater, both vomiting (87.5%) and defecation (75%) usually occurred in a single episode which ended within approximately 15 minutes. No studies of the efficacy of gastric emptying by this method as compared to apomorphine are known. Prostaglandin F2-α causes increases in respiratory rate and airway resistance, such that animals with respiratory disease may be at an increased risk of complications if this agent is used.

Salt - The emetic mechanism of dry salt is pharyngeal stimulation. **NaCl is not a reliable emetic and may result in salt poisoning in small animals**. Saline solutions have been shown to be only 25% as efficacious as ipecac in inducing vomiting in humans. The development of hypernatremia has been reported to occur in humans in which salt had been used as an emetic. Secondary to the development of severe hypernatremia will be the development of cerebral shrinkage as water is drawn out of the brain tissue. Intracranial blood vessels expand and secondary intraventricular and brain hemorrhage has been reported in human patients. Terminally, cerebral edema has been documented in sodium toxicosis of animals. Clinical signs of salt intoxication can include weakness, vomiting, seizures, tachycardia, and pulmonary edema. **Note**: Ingestion of 1 tablespoon of salt (contains 250 mEq of sodium) by an animal with a 10-liter total body water (e.g., 15-kg dog) can result in an increase in serum sodium by 25 mEq/l. Salt water has also been recommended but is probably even less effective and is far too dangerous to recommend.

Hazards of Salt as an Emetic - Summary of Reported Deaths in Man								
Case	**Age**	**Gender**	**Drug Ingested**	**How Salt was Administered**	**Did Vomiting Occur ?**	**Maxim. Na**	**Serum Cl**	**Time Until Death**
1	74	M	60 mg perphenazine 750 mg imipramine	1 T/300 ml water x2	yes	174	152	32 hr
2	35	F	5000 mg thioridazine	3000 mEq /4000 ml water x1	?	184	150	8 days
4	3	M	250mg propoxyphene	4 T/8 oz water x 4	yes	189	156	9 days
4	3	M	2900 mg aspirin	? amt x2	no	188	160	28 hr
5	23	F	? mg chlordiazepoxide	?	?	214	-	18 hr

Based on the evidence at hand, salt water is too dangerous to recommend for use either at home or in the emergency room.

Gastric Lavage

Emesis vs. lavage: whenever the patient's condition allows emesis to be induced, the greater efficacy of vomiting in removing stomach contents, the greater ease of administering an emetic, and the more satisfactory removal of sizable amounts of particulate matter or tenacious mucus by vomiting, all favor emesis over lavage. In dogs which were administered barium sulfate orally, emesis (ipecac, apomorphine) was equally effective as gastric lavage (mean of 78%, 62% vs. 54% recovery rates, respectively) when administered immediately. However, a significant difference was noted if these procedures were delayed. If delayed 30 minutes, recovery rates were apomorphine 64%, ipecac 44%, and lavage 26%. By 60 minutes postingestion, lavage was only 8% effective. Research by others has demonstrated that gastric lavage is less effective than emesis in recovering toxicant whether administered immediately or following a delay after ingestion.

Proponents of gastric lavage suggest that in many of these studies lavage was performed incorrectly. To adequately perform gastric lavage, **large bore gastric lavage tubes** (e.g., foal stomach tube could be substituted) **and copious amounts of lavage fluid** are required. Other factors that influence the efficacy of lavage are: **1**) lavage fluid temperature (tepid water preferred, colder water increases gastric emptying time), **2**) agent ingested, and **3**) frequency of lavage. Increased gastric emptying time could be desirable in some situations (i.e., toxicant in stomach not absorbed from stomach but from GI).

When potent toxicants have been ingested and vomiting has not been intense, lavage may be worthwhile. Lavage may also be indicated in the ingestion of agents in which delayed gastric emptying is anticipated (e.g., tricyclic antidepressant ingestion). Of course gastric lavage is used in many cases in which the patient cannot safely be made to vomit as previously mentioned; for example, if the patient is comatose and a toxicant ingestion is suspected. Gastric lavage is **contraindicated** in the ingestion of caustic materials and for seizuring animals unless the animal has been anesthetized and will be continuously monitored.

Technique for Gastric Lavage

Note - Minimal pressure should be used since the stomach wall may be weakened.

The procedure is performed on unconscious or lightly anesthetized animals (watch fingers). An **endotracheal tube (cuffed) is inserted and inflated to avoid aspiration** of stomach contents. A 2 - 4 foot-long clear plastic tube with **as large a diameter as possible** and having the end fenestrated with one or two oblong holes is used. A smaller tube or loop ended wire is handy to clean out stomach tubes after they have been removed from the animal. It may also help to alternate stomach tubes, one in use, one being cleaned out. One also needs to have available funnels, buckets, aspiration bulbs for extremely small animals and a drench (bilge) pump for all others.

The tube is inserted to a length equivalent to the distance from the tip of the nose to the xiphoid cartilage. After the stomach tube is in place, the mouth should be kept lower than the chest (tilt table). A watery activated charcoal suspension is recommended for the lavage fluid **after the initial washings have been collected** for analysis. Gently creating turbulence by pumping the fluid in under slight pressure as from a bilge pump, mixes the contents near the end of the tube allowing gradual removal by gravity flow. Several cycles (perhaps 15 - 20) of 50 - 200 ml (5 - 10 ml/kg) each may be required to thoroughly rinse out the stomach. The last few washings should be clear. The end of the tube should be closed as the tube is removed in order to prevent aspiration. A thicker activated charcoal suspension is instilled after either gastric lavage or cessation of vomiting.

Enemas

Enemas may be occasionally indicated in cases where absorption has not been completed in the upper GI tract. Enemas also facilitate the effects of cathartics. A solution of warm water and castile soap (available at many groceries, pharmacies) is sometimes recommended. Patients with an increased potential for renal failure should not receive phosphate enema solutions because of the possibility of precipitating acute renal failure. Such solutions have sometimes been recommended for oral administration as a saline cathartic or to precipitate ingested iron. In addition, hypertonic phosphate enemas (e.g., fleet enema) when used in cats and small dogs may result in severe toxicosis due to rapid electrolyte (hyperphosphatemia, hypernatremia, hypocalcemia, hypomagnesemia) and acid-base (metabolic acidosis) disturbances.

Enterogastric Lavage

This technique may be used to remove the entire contents of the gastrointestinal tract. However, it is not regarded as practical and has not been demonstrated to be safe or effective (and hence is not recommended) for animals with highly modified, high volume digestive tracts such as ruminants, horses, rabbits and swine (spiral colon). First, an emetic is used if not contraindicated, then minimal anesthesia is induced and a standard gastric lavage performed, leaving the endotracheal and gastric tubes in place. Second a moderately high, warm water enema is used. Mild digital pressure is then applied around the enema tube at the anus and water is administered slowly using a colon tube with a faucet adaptor and low pressure to cause retrograde filling of the intestine. The water is gradually added until it is clear as it flows from the gastric lavage tube. By the time that fluid comes from the stomach tube, the intestinal loops may be substantially enlarged by the water. Activated charcoal may be instilled at the end of the procedure.

Rumen Lavage and Rumenotomy

Rumen lavage is much more rapid and far less work then rumenotomy, however to be efficient, access to tap water is almost essential. The procedure is usually performed on conscious, standing animals. A head stanchion should be used if possible. The use of a chute is **not** recommended because when cattle lie down, as they often do when in a chute, you cannot accurately judge rumen distension. Excessive distention of the rumen can compromise ovement of the diaphragm resulting in sudden death. If possible, place the animal on a sloped incline so that the head is below the body. A large stomach tube is passed with a mouth gag. A slightly smaller tube, such as a garden hose with or without a nozzle, that just fits inside the stomach tube is used as a connection to the water faucet. Water flowing rapidly from the smaller tube is directed into the large tube by slipping the smaller one inside for just a few seconds. The water is then allowed an opportunity to run back out. Often the first infusion or two will not be returned. However, by the time distension of the paralumbar fossa is evident, water should be running back out after each administration. This is continued until the water is clear, then activated charcoal is administered. Toxicoses involving ingestion of coarse toxic plant material (e.g., Taxus, Rhododendron) will probably required rumenotomy. In situations in which few animals are poisoned and in which rumen lavage cannot be performed and in situations in which activated charcoal is unavailable or unlikely to be successful, rumenotomy may be considered.

An alternative to the use of rumen lavage or rumenotomy is the use of a large bore (3/4") diameter **trochar** which is inserted into the rumen at the **level of the stifle**. A hose is employed as in rumen lavage, and rumen contents exit the rumen via the trochar. The trochar is left in place for at least 5 days in order to allow the rumen to form an adhesion to the body wall resulting in a decreased risk of peritonitis. This technique has been used clinically in the management of acute grain overload in cattle.

Gastrotomy

On rare occasion, a gastrotomy may be required in order to remove foreign bodies from the stomachs of small animals. Examples of cases in which gastrotomy should be considered include metal ingestions (e.g., lead weights, pennies, zinc bolts, etc.) or rarely large quantities of ingested drugs which form coalesced masses (e.g., meprobamate). Although this method is effective, if used **should be considered heroic** and reserved only for cases where more conservative methods have failed or are likely to fail. An alternative to gastrotomy would be **endoscopic retrieval**, use of an endoscope and appropriate probes to disrupt masses or remove foreign bodies from the stomach may be preferred.

Note - any of these techniques must be weighed against the stress associated with both the necessary restraint and the actual detoxification procedure.

Osmotic Cathartics

Sodium Sulfate or Magnesium Sulfate (Saline Cathartics) - The effectiveness of sodium sulfate and magnesium sulfate have been attributed to their poor or slow rate of absorption which results in osmotically induced fluid retention within the intestinal tract. The laxative effect results from reflex stimulation of motility caused by the increased intraluminal fluid volume. The sulfates of both sodium sulfate and magnesium sulfate are, however, absorbed to a greater extent than generally recognized. It is also known that, in the presence of renal disease, sufficient magnesium may be absorbed to produce clinical signs of hypermagnesemia, including muscle weakness and depression of the central nervous system. The concurrent use of a cathartic with activated charcoal has not been demonstrated to decrease absorption of an agent over the effect of activated charcoal alone. In evaluating whether a saline cathartic should be administered, several factors should be considered: **1**) saline cathartics should not be administered if the ingested agent will have similar cathartic effects (e.g., laxative ingestions); **2**) some formulations (e.g., enteric coated, microencapsulated) may have decreased bioavailability if a cathartic is administered; **3**) activated charcoal may cause constipation and cathartics may minimize this effect. Magnesium (in magnesium citrate) and sulfate are poorly absorbed to activated charcoal and are **not** thought to interfere with its adsorptive capacity.

Sodium sulfate (Glauber's Salt) is a more efficient saline cathartic then magnesium sulfate (Epsom Salt). Also the magnesium ion can depress the CNS. Magnesium sulfate is, however, more widely available and for some toxicoses the depressant effects of the magnesium ion may be of no harm or even of benefit. Using the contents of an ordinary teaspoon (the kind used to eat, not to measure) the following weights were derived for level teaspoons.

Weights determined in grams for "level teaspoons" of	
Sodium sulfate (Glauber's Salt)	**Magnesium sulfate (Epsom Salt)**
9.12	7.11
8.32	6.98
8.03	6.43

The dose of sodium or magnesium sulfate for dogs and cats is therefore 1/4 teaspoon (approx. 1.75 - 2 grams) per 10 pounds (4.54 kg) of body weight (this is approximately equivalent to 385 - 440 mg/kg BW). It is administered per os preferably by stomach tube as a 20% (or more dilute) solution in water. One of the principle benefits of sodium sulfate is mixing of the gastrointestinal contents when administered concurrently with activated charcoal. The **combination** is **far more effective than** the **cathartic alone** and may be significantly better than the charcoal alone. If charcoal is to be given repeatedly, the first two doses are generally accompanied by either a saline or osmotic cathartic.

Magnesium Hydroxide or Magnesium Citrate - Other osmotic cathartics include magnesium hydroxide (Milk of Magnesia) and magnesium citrate. Although not proven of benefit, magnesium hydroxide is recommended for animals that have ingested zinc phosphide. Dosages are shown in Table I-8.

Sorbitol - Sorbitol is sometimes used as a cathartic. At the present time, a product called Superchar-vet® is marketed in liquid form for small animals. The product contains a highly activated charcoal and sorbitol.

Table 2. The following total doses for cathartics have been recommended						
	Horse	**Cow**	**Sheep & Goat**	**Pig**	**Dog**	**Cat**
Magnesium sulfate	250 - 100 g	250 - 100 g	25 - 125 g	25 - 125 g	5 - 25 g	2 - 5 g
Sodium sulfate	250 - 375 g	500 - 750 g	60 g	30 - 60 g	5 - 25 g	2 - 5 g
Magnesium oxide	-	500 g	5 - 10 g	5 - 10 g	0.5 - 4 g	0.2 - 1 g
Magnesium hydroxide susp.	1 - 4 liters	1 - 4 liters	20 - 150 ml	10 - 50 ml	5 - 10 ml	2 - 6 ml
Mineral oil	250 - 100 ml	250 - 500 ml	15 - 150 ml	25 - 300 ml	5 - 30 ml	2 - 6 ml
Sorbitol (70%)	-	-	-	-	1 mg/kg	1 ml/kg

Bulk Cathartics

Metamucil® (psyllium), a hydrophilic mucilloid-based laxative is sometimes of value for animals exposed to toxicants or physical agents that may need some bulky material to gently encourage their passage (e.g., lead objects, fiberglass insulation, sand, etc.). Forms of the laxative that do **not** contain sugar are preferred for this purpose.

Oily Cathartics

Oily cathartics including mineral oil and olive oil are not clearly indicated for organochlorine insecticides and other organic compound ingestions, since they are often less effective than other measures, such as the use of activated charcoal with a saline cathartic, with regard to diminishing the toxicant's absorption. Oils are nevertheless, still recommended for preventing the absorption of certain other toxicants. Mineral oil is recommended for phosphorus toxicosis, but it must be carefully administered to avoid aspiration. Mineral oil administration may be followed by a saline cathartic. Surfactants such as the stool softener dioctyl sodium sulfosuccinate (DOSS) may be contraindicated with mineral oil administration as emulsification of the oil may contribute to its absorption and therefore accumulation of the indigestible oil in the liver. Castor oil is likely to pass through the intestine more rapidly than mineral oil and in some toxicoses has been more effective than mineral oil in reducing absorption.

Irritant or Stimulation Cathartics: These agents are not recommended for poisoned animals.

c. Trapping the Poison in the GI Tract

Activated Charcoal - Activated charcoal will adsorb to many substances to prevent absorption. See Tables I-9 and I-10. Indications for the administration of activated charcoal include: **1**) toxicant ingestions, **2**) endotoxins, and **3**) agents which may undergo enterohepatic elimination or recirculation (e.g., some topically applied pesticides). Animal studies evaluating oral and topical exposure to activated charcoal have shown a lack of toxicity of the adsorbent.

Activated charcoal is considered to be a nonspecific adsorbent. Attachment to the surface of the activated charcoal is accomplished through nonspecific weak forces. The number of drug or toxin molecules that can be adsorbed varies but sometimes is approximately proportional to molecular size.

Inactivation of a compound by charcoal is not equivalent to chemical destruction. Ionized solutes are less firmly adsorbed than neutral solutes. Nonpolar large molecules are most rapidly adsorbed. Nevertheless, even in the case of a small, uncharged, rapidly-adsorbed molecule like ethylene glycol, the addition of activated charcoal to the treatment regimen is reportedly beneficial only when given within 6 hours after oral exposure.

Table 3a. Efficacy of Activated Charcoal

Substance	Maximal Adsorption per Gram of Activated Charcoal
Mercuric Chloride	1800
Strychnine Nitrate	950
Nicotine	700
Barbital	700
Phenol	400

Table 3b. Other Compounds Adsorbed by Activated Charcoal

Acetaminophen	Ergotamine	Paracetamol (Acetaminophen)
Aconitine	Ethchlorvynol	Parathion
Alcohol	Glutethimide	Penicillin
Amphetamines	Hexachlorophene	Phenolphthalein
Antimony	Imipramine	Phenothiazines
Antipyrine	Iodine	Phenylbutazone

Arsenic	Ipecac	Phenylpropanolamine
Aspirin (salicylate)	Isoniazid	Phenytoin
Atropine	Kerosene	Phosphorus
Barbiturates	Lead	Potassium Permanganate
Bromethalin	Malathion	Primaquine
Camphor	Mefenamic Acid	Probenecid
Cantharides	Meprobamate	Propantheline
Carbamazepine	Mercury	Propoxyphene
Chlordane	Methyl Salicylate	Quinacrine
Chloroquine	Methylene Blue	Quinidine
Chlorpheniramine	Morphine	Quinine
Cocaine	Muscarine	Salicylamide
Colchicine	Nicotine	Salicylates
Cyanide	Narcotics	Selenium
Diazepam	Nortriptyline	Silver
2,4-Dichlorophen-	Opium	Stramonium
Oxyacetic Acid	Organophosphorus	Strychnine
Digitalis	Insecticides	Sulfonamides
Digitoxin	Organochlorine	Tin
Diphenylhydantoin	Insecticides	Tricyclic antidepressants
-	Oxalates	-

Note - Many other substances also adsorb to activated charcoal.

Compounds with Little or no Absorption		
Alkali Boric Acid	Ferrous sulfate	Mineral acids

Activated charcoal is created through 2 general steps: pyrolysis followed by controlled oxidation. The activated charcoal should be of vegetable origin and not be mineral or bone charcoal. The initial processing of activated charcoal produces a product with large pore size. Further "activation" increases pore number and surface area. Acceptable brands (manufacturer) include: Norit A (American Norit Company), Nuchar (West Virginia Pulp and Paper Company), Darco 60 (Atlas Chemical Company and Fischer Scientific), Carbo Med (Merck), and Toxiban (Vet-A-Mix). The latter product is 70% activated charcoal, 8% kaolin, and 22% wetting and dispersing agents to facilitate administration. Recently, a new superactivated charcoal (Superchar-Vet), the small animal version of which contains an osmotic cathartic (sorbitol), has become available. This product has about a 3 times greater adsorptive capacity than other activated charcoals. Burnt toast is essentially inert and should not be used as a substitute for activated charcoal.

Maximum prevention of toxin absorption occurs when a sufficient amount of charcoal is administered and the time interval between toxicant ingestion and administration of charcoal is brief. Activated charcoal powder as a suspension in water is administered orally or by nasogastric (gastric, rumen) tube. Charcoal tablets or universal antidotes are not as effective. Charcoal tablets are approximately 25% less absorptive than powders. The so-called "universal antidote", long suspected of being an irrational mixture is, in fact, less effective than activated charcoal alone. The mixture contains 2 parts activated charcoal, 1 part magnesium hydroxide and 1 part tannic acid. It is entirely irrational to combine activated charcoal with an oily cathartic, such as mineral oil, which greatly diminishes the adsorptive capacity of the charcoal. Administration of milk or flavoring agents should be avoided when activated charcoal is given.

The dosage for most activated charcoals for cattle is 1 kg per 500 kg of body weight. Bulk sources are needed where herds of animals are involved. Although the cost of some activated charcoals is prohibitive for large animals, DARCO S-51 (ICI Americas, Wilmington, DE.) costs approximately $1.00/kg when purchased in ton quantities. Depending upon the toxicant involved, therapy may need to be repeated every 6 hours, daily, or every other day. Activated charcoal may sometimes be mixed into the feed of large animals. The Superchar® and Toxiban® formulations are conveniently made up as a liquid for small animals and in powdered form for large animals. Of the two, the former is likely to be more effective.

The dosage of activated charcoal for small animals is 1 - 4 gm/kg of body weight in 50 - 200 ml of H_20 or 5 heaping teaspoons in 200 ml water for a 30 pound dog. Twenty to thirty minutes following the administration of the charcoal (if there is not an osmotic cathartic present as in the Superchar small animal product) a saline cathartic is often administered. After using charcoal, emetics must be administered parenterally.

Activated charcoal given repeatedly may be of benefit in interrupting enterohepatic recycling of certain xenobiotics. Its use is seldom if ever economically practical for causing depletion of tissue residue from food animals. There is also a possibility of "gut dialysis", which suggests that, by means of repeated activated charcoal administration, the lumen can act as a "sink" or trap with the toxicant passing across the mucosa to be bound by the adsorbent. Evidence for diminished bioavailability exists in humans in which the half-life and volume of distribution of **intravenously** administered digoxin was decreased by oral administration of activated charcoal.

The half-life of phenobarbital is decreased from 100 hours to less than 20 hours with the repetitive administration of activated charcoal during a 24 - 72-hour time period. Similar reductions have been reported for humans poisoned by digitoxin (highly excreted in the bile-unlike digoxin), nortriptyline, carbamazepine, phenylbutazone, and caffeine.

Clay or Bentonite - Kaolin, a clay, is hydrated aluminum silicate. Pectin is a purified carbohydrate from acid extraction of citrus fruit rinds or apple pomace. The combination is dissolved in 70 parts water as kaopectate. Kaolin is also an ingredient, with activated charcoal, in Toxiban®. Bentonite is colloidal hydrated silica. Like kaoline, bentonite is a simple clay. Kaolin-pectin (kaopectate) has been used as a demulcent and adsorbent in the treatment of some toxicoses. Kaopectate is generally dosed at 10 - 50 ml/dog. In general, activated charcoal is far superior to clays as an adsorbent although clays are better adsorbents than activated charcoal for paraquat.

Ion Exchange Resins - A primary pharmaceutical use of certain members of this group is to lower blood cholesterol by binding bile acids in the intestine lowering cholesterol absorption. Similarly the absorption of other fat soluble substances such as certain organochlorines is reduced. Some of the more widely used ion exchange resins also bind other acidic anions. Acidic drugs or toxins bound in the resin are then lost in the feces. Neutral or basic compounds are less firmly bound. Ion exchange resins are not truly adsorbents since the binding of agents to their available binding sites is by ionic bonds (vs. weak nonspecific forces involved with charcoal adsorption). The powdered products are mixed with water before use, and may be mixed in food. Their use may result in constipation (severe if used excessively). Oral fluids and a bulky diet are therefore encouraged to prevent constipation.

The ion exchange resins may delay or reduce the absorption of phenylbutazone, warfarin, chlorothiazide, tetracycline, phenobarbital, thyroid preparations and digitalis glycosides. One product, cholestyramine resin (Cumid® and Questran®) has been successfully employed to interrupt the enterohepatic recycling and to shorten the half-life of digitalis in poisoned patients. Cholestyramine is the chloride salt of a basic anion exchange resin. Cholestyramine must be mixed with water or other fluids before ingestion, it should not be administered in the dry form. Doses of 200 - 300 mg/kg have been suggested for humans and extrapolation to animals from this dose may be reasonable. Potential side effects of cholestyramine include hypochloremic acidosis (overdose), steatorrhea, loss of fat-soluble vitamins, constipation, and hypoproteinemia. Another ion-exchange resin is cholestipol HCl (Colestid®).

Kaexolate® is an ion exchange resin used to reduce excessive serum potassium by binding potassium in the gut in exchange for sodium.

Bismuth Subsalicylate - Bismuth compounds are demulcents and weak adsorbents and will bind to ulcerated mucosae. Bismuth subsalicylate (in Pepto-Bismol®) is also reported to have antiprostaglandin effects. These compounds' main benefit is in the treatment of diarrhea produced by enterotoxigenic organisms. Bismuth compounds may have some benefits as a symptomatic therapy for poisoned animals (but should be avoided if antiprostaglandin agents, e.g., aspirin, nonsteroidal anti-inflammatory drugs, have been ingested). A common dosage recommendation for Pepto-Bismol® is 1 ml/kg. Salicylate toxicosis (hyperventilation, hyperthermia, acidosis) is of concern for the salicylate in Pepto-Bismol® is absorbed (cat especially sensitive).

Formation of Insoluble Complexes in the Gut - Oral magnesium or sodium sulfate treatment for lead or barium exposure causes formation of insoluble lead sulfate or barium sulfate thereby preventing absorption. Note: Soluble salts of barium are highly toxic. Calcium solutions may be given orally for soluble oxalic acid or oak which contains gallotannins (gallic and tannic acids). sodium bicarbonate lavage solutions may be used in iron poisoning since sodium bicarbonate converts ferrous ion to ferrous carbonate which is poorly absorbed. Sodium formaldehyde sulfoxylate has been recommended in mercuric chloride ingestions since mercuric salts are reduced to less soluble metallic mercury.

Alkaloid Inactivation - Tannic acid has been previously recommended for certain alkaloid toxicoses but not for cocaine, nicotine, physostigmine, atropine, or morphine. When administered, tannic acid must not be left in the stomach; it is removed by catharsis or emesis. A previously recommended dose of tannic acid for small animals is 200 - 500 mg in 30 - 60 ml of water. It is becoming more widely accepted that the **risk of tannic acid toxicosis may sometimes outweigh the benefit derived**. Tannic acid causes centrilobular necrosis of the liver. The previously recommended dose in large animals was 5 to 25 gm in two to four liters of water. Potassium permanganate (1:5,000 to 1:10,000) is therefore, preferred for lavage and/or administration after alkaloid ingestion. For many alkaloids, however, activated charcoal can be substituted and it is much more often available.

d. Removal of Poisons after Ocular or Topical Exposure

For **ocular exposure**, have the client flush the eyes with copious amounts of warm water. Caution regarding restraint of the animal is mandatory for the owner's protection. **Irrigation of chemically damaged eyes should never be delayed**. Water or physiological saline solutions are first choices. The use of neutralizing agents is not recommended. **A minimum of 20 - 30 minutes** of irrigation is recommended. The animal should be examined as soon as possible thereafter. Following adequate irrigation, chemical burns to the eye are treated with lubricant ointments and lid closure techniques (e.g., third eyelid or conjunctival flap) to protect the damaged surface. atropine may be considered as a cycloplegic agent. Close follow-ups are required since epithelial damage may be delayed (especially with alkali burns).Corticosteroids should be used only if the corneal epithelium is intact.

For **dermal exposures** of small animals or individual large animals, start with a liquid dish detergent for oily substances (e.g., insecticide preparations). Repeat baths until the insecticide odor is reduced as much as possible or eliminated. Rinse very thoroughly with copious amounts of water. Rubber gloves and plastic aprons should be used to avoid exposure of the person bathing the animal. Avoid greasy topical medications as they may act as a vehicle to enhance absorption. Solvents may do more harm than good as they disperse the chemical, increase the exposed surface area and alter the permeability of the skin.

To remove asphalt or sticky traps used to control or monitor insect and rodent populations, polysorbate 80 containing cremes may be used, but butter may be equally effective and much less expensive. Alternatively, a mechanic's hand degreaser (e.g., Goop®) may be quite effective. These agents may also be effective in removing oil-based paint from animals. Naturally, this is followed by a thorough bath.

For dermal exposures of significant numbers of large animals, crowding the animals together in a small pen is followed by wetting with a power sprayer or high-pressure hose. This is followed by the use of one of the less irritating powdered laundry detergents and a subsequent thorough rinse.

The following has been recommended for deodorizing the skunk-affected pet: 1 quart 3% hydrogen peroxide, 1/4 cup baking soda (sodium bicarbonate) and 1 teaspoon liquid soap. The bath should be followed by a tap water rinse. The animal should **not** be allowed to swallow the mixture. Do not use near heat source or open flame due to the release of oxygen.

6. Facilitating Removal of Absorbed Toxicants

The next concern is the systemic poison that has already been absorbed. Active methods for the removal of absorbed toxicants would include methods to: **1**) enhance metabolism to less toxic forms, **2**) increase excretion rates of toxin, or **3**) direct removal of a toxicant from the affected animal (e.g., hemofiltration). Enzyme-inducing drugs such as phenobarbital take at least a couple of days to significantly increase mixed function oxidase activity. Therefore, they have been recommended for use in reducing residues of persistent xenobiotics in tissues but, comparative studies have failed to demonstrate significant economic benefit. More importantly, for most acutely poisoned animals, the enzyme-inducing effect is often too late. A concern also exists if enhanced microsomal enzyme activity may lead to increased metabolism of compounds activated by mixed function oxidases. Specific antidotal therapies (e.g., alcohol dehydrogenase inhibitors with ethylene glycol) are occasionally employed to modify the metabolism of a toxicant.

As a result of the limited role for enhanced metabolism, attention must be focused on ways of promoting excretion. The urinary tract and biliary tract represent the two principle routes by which exogenous chemicals are most commonly removed. Interrupting enterohepatic recirculation with periodic administration of activated charcoal or ion exchange resins has already been mentioned.

a. Forced Diuresis

Clinical indications for measures to promote renal elimination of absorbed toxicants include: **1**) presence of serious clinical toxicosis with clinical signs (e.g., severe hypotension, coma, arrhythmias), **2**) potentially lethal dose has been ingested, **3**) impairment of normal route of excretion (e.g., organ injury, concentration-dependent elimination rates), **4**) progressive deterioration of an animal's clinical condition in the face of intensive therapy.

The use of forced diuresis may be associated with the following complications: **1**) pulmonary edema, **2**) cerebral edema, **3**) metabolic acidosis or alkalosis, **4**) electrolyte imbalances (e.g., hyponatremia, hypokalemia), and **5**) water intoxication. For these reasons, vigorous attempts at **forced diuresis should be limited** to situations in which benefit can be expected.

Promotion of renal excretion of toxicants is frequently very beneficial to the patient and is heavily relied upon in the management of many toxicoses. However, diuresis is of benefit only for compounds which are present in significant concentrations in the plasma. In general, organic acids are present in plasma in greater concentrations than organic bases due to the fact that, the plasma is slightly alkaline compared to the intracellular environment, which results in partitioning. Nonpolar compounds which tend to resist biotransformation, such as dieldrin or kepone are present in plasma in such low concentrations that diuresis is of little benefit for increasing their excretion.

The composition of urine is determined by the combined processes of: **1**) ultrafiltration, **2**) active tubular secretion, and **3**) passive tubular reabsorption. In the glomerular tufts, toxicants which are not bound to albumin will be ultrafiltered. Active transport systems are present in the proximal convoluted tubules which can transport some drugs or toxicants. Separate transport systems exist for basic and acidic agents. Tubular reabsorption of foreign substances is limited to unionized lipid-soluble agents and is largely passive. Indirectly, however, this passive migration is a consequence of the active tubular transport of sodium chloride. This is because the tubular fluid (glomerular filtrate) tends to become concentrated with respect to all solutes not actively resorbed during this process. In general, excretion of toxic substances is promoted by taking steps necessary to minimize passive tubular reabsorption of toxic solutes.

The effect of administration of water (water diuresis) on the excretion of most substances is minimal. An increased water load inhibits ADH secretion, but the principle effects of ADH are on the volume and flow in the distal tubules and collecting ducts. Most passive resorption occurs in the proximal tubules.

b) Osmotic Diuretics

Osmotic diuretics reduce water resorption in the proximal convoluted tubules and prevent the concentration of passively resorbed substances at this site. This reduces renal toxicity and promotes excretion.

Mannitol - Mannitol is one of the most commonly used osmotic diuretics. It does crystallize and is sometimes hard to dissolve (immerse in hot water). Therefore, it is wise to store unopened vials away from cold walls, etc. Mannitol is infused intravenously as a 20% solution at a rate not to exceed 0.5 grams per kg the first hour. This should increase urine flow. The diuresis should continue with 5% mannitol in Ringer's solution since mannitol diuresis also increases the excretion of sodium and potassium. Supplementation of Ringers with potassium could be considered.

If either glomerular or tubular function is too severely compromised, mannitol will not increase urine flow. Mannitol should not be administered to anuric animals. Infusion of 5% mannitol at a rate of approximately 10 ml/kg/hour should at least triple urine flow. Urinary output and body weight should be measured to avoid overhydration and pulmonary edema.

Mannitol has also been recommended to reduce the pressure and volume of the cerebrospinal fluid. Mannitol is distributed in the extracellular fluid. Administration is therefore accompanied by an expansion of the extracellular fluid volume. In the patient with cardiac decompensation, this represents an undesirable hazard. Marked pulmonary congestion or edema, dehydration, and intracranial hemorrhage are additional contraindications to the use of mannitol.

Urea - Urea may be used as an osmotic diuretic at a dose rate one-half that of mannitol.

50% Dextrose **-** Concentrated dextrose is also effective, inexpensive and provides a small amount of energy to the animal. Provided it is kept free of bacterial contaminants, it is one of the safest osmotic diuretics. With any osmotic diuretic, fluids are required to maintain hydration.

c) Water Loading and Other Diuretics

In large animals such as cattle and horses, when it is difficult to obtain the large volumes of solutions necessary for infusion it is sometimes practical to pump fairly large volumes of water or nonsterile electrolyte solutions into the rumen or stomach. This will increase urine flow and, in this circumstance, the judicious use of potent diuretics such as furosemide may enhance diuresis. In other toxicoses, in which renal shutdown does not respond to osmotic diuresis, a single dose of furosemide may also be warranted.

d) Ion Trapping

The basic premise of ion trapping is that ionized compounds do not readily traverse cell membranes and are therefore not resorbed by the renal tubules. Many chemicals, particularly drugs, are weak acids or weak bases. Note the ratio of nonionized to ionized drug is calculated from the Henderson-Hasselbach equation; pH = pKa + log [salt]/[acid]. At a pH equal to the pKa, an agent will be 50% ionized and 50% nonionized. If the urinary pH favors the ionized form, an agent becomes "trapped" in the tubular fluid and is more likely to be excreted. Acidic compounds such as aspirin remain ionized in alkaline urine and alkaline drugs such as amphetamines are ionized in acidic urine. Generally alkaline urine therefore favors increased excretion of acidic drugs and vice versa.

For an agent to respond to pH manipulation of the urine, the following criteria must be met:

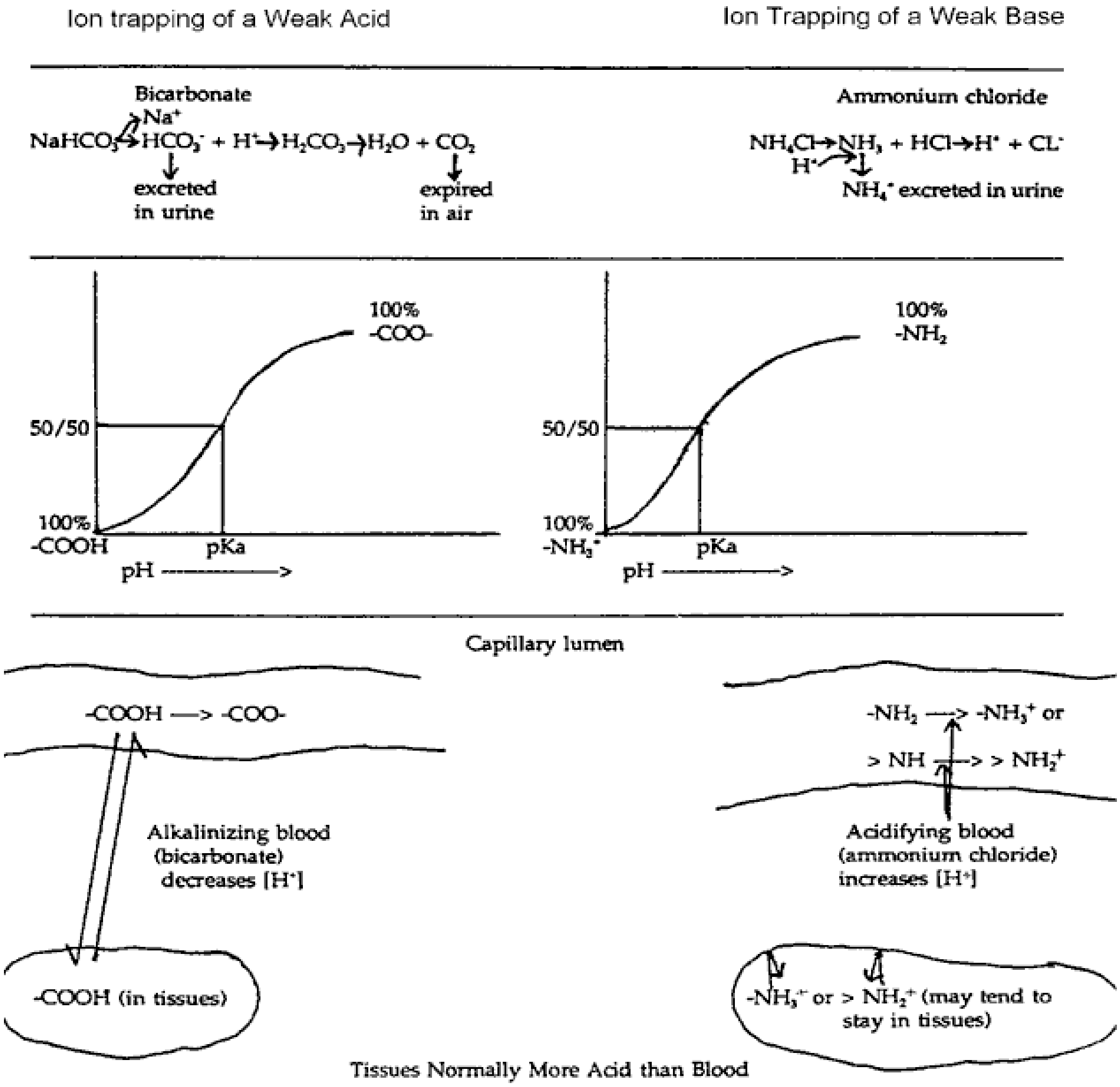
1) the toxicant or its toxic metabolite(s) must be significantly eliminated by the kidneys in an unconjugated form, **2**) the agent or its toxic metabolite(s) must have a pKa (acidic or basic) that is in the range of common urinary pHs, and **3**) the agent must not be extensively protein bound and is not highly lipophilic. Ammonium chloride (100 mg/kg in dog or 20 mg/kg in cat, BID) or chlorethamine are used orally to acidify the urine. Administration of ammonium chloride requires monitoring of metabolic status and is contraindicated if hepatic or renal insufficiency is present. Acidification of the urine is also contraindicated if severe rhabdomyolysis or myoglobinuria is present. The nephrotoxicity of myoglobin is considered to be enhanced in acid urine. Ammonia intoxication can also develop and is most often manifested by depression and coma. Plasma potassium and urine pH should be monitored frequently. Acid diuresis of human patients is presently limited to amphetamine (pKa = 9.9), phencyclidine (pKa = 8.5), guinine (pKa = 8.4), strychnine (pK_1 = 6.0, pK_2 = 11.7), and fenfluramine (pKa = 9.9) overdoses. A urine pH of 5.5 - 6.5 is usually maintained.

Forced alkaline diuresis is generally achieved with sodium bicarbonate at 1 - 2 mEq/kg administered intravenously every 3 - 4 hours. The goal in man for urine pH is 7.0 or greater. Carnivores tend to have more acidic urines, however, and excessive attempts to increase urinary pH to this point may result in metabolic alkalosis. The use of alkalinization may require the correction of associated potassium and chloride deficits. Bicarbonate is of considerable benefit in ethylene glycol toxicosis.

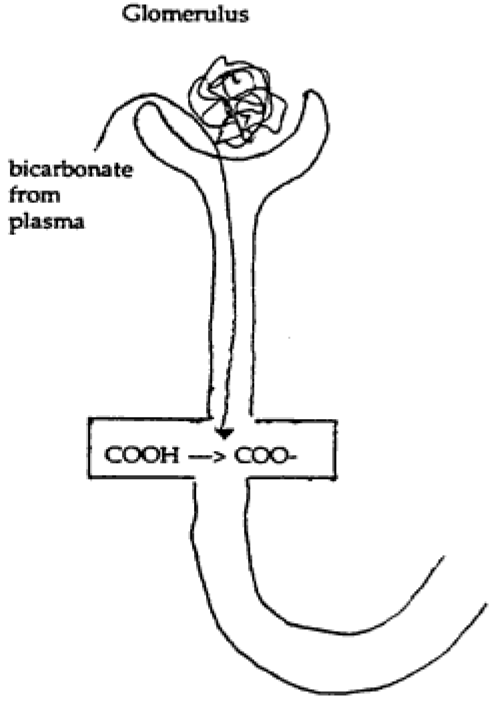
To alkalinize urine, one must exceed the renal threshold for bicarbonate of 24 mEq/liter. It is suggested that blood bicarbonate be increased by 40 - 50%. This would require 2.0 mEq HCO_3/kg. sodium bicarbonate should be infused intravenously at a very slow rate or, better, may be added to fluids for infusion. The administration of lactated Ringer's solution, to which mannitol or urea is added is effective for enhancing excretion of barbiturates. The addition of bicarbonate would be expected to further enhance excretion. Alkalinization of the urine has been used successfully to treat salicylate, phenobarbital, and 2,4-dichlorophenoxy acetic acid (2.4-D) poisonings.

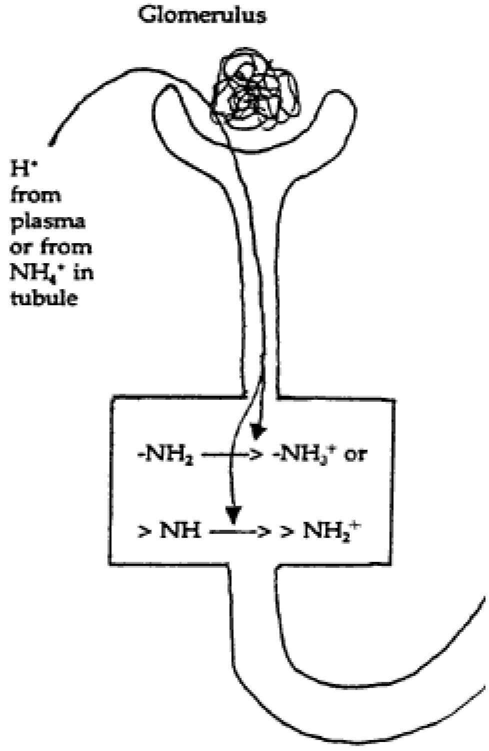
Note: Strong bases (pKa greater than 8.0) and strong acids would tend to be already charged in the glomerular filtrate and therefore readily excreted by the kidney **without modifying the pH**.

Principles of Ion Trapping


Ion trapping of a Weak Acid
Ion Trapping of a Weak Base
Bicarbonate
Na+
NaHCO3 → HCO3- + H+ → H2CO3 → H2O + CO2
excreted in urine
expired in air
Ammonium chloride
NH4Cl → NH3 + HCl → H+ + CL-
H+
NH4+ excreted in urine
100% -COO-
50/50
100% -COOH
pKa
pH ——————>
100% -NH2
50/50
100% -NH3+
pKa
pH ——————>
Capillary lumen
-COOH —> -COO-
Alkalinizing blood (bicarbonate) decreases [H+]
-COOH (in tissues)
-NH2 —> -NH3+ or
> NH —> > NH2+
Acidifying blood (ammonium chloride) increases [H+]
-NH3+ or > NH2+ (may tend to stay in tissues)
Tissues Normally More Acid than Blood

Principles of Ion Trapping (Continued)





e) Dialytic Techniques for Toxin Removal

Dialysis is used to describe the movement of an agent across a semipermeable membrane. The effectiveness of a dialytic technique depends upon the toxin's size (smaller sized more easily dialyzed), lipid solubility, protein binding, volume of distribution, and the presence of a concentration gradient, in addition to blood flow rates and dialysate characteristics. **Dialysis should be considered if renal failure is present** or if large quantities of a toxicant are present.

Peritoneal Dialysis - In peritoneal dialysis the large surface area of the peritoneum serves effectively as a membrane for exchange of diffusible substances of varying molecular weight. Fluid placed within the peritoneal cavity becomes an extension of the extracellular fluid compartment and at equilibrium will have an identical composition of solutes as present in the blood perfusing the abdominal viscera. Six hours of peritoneal dialysis may be equivalent to 12 hours of hemodialysis using an artificial kidney. The most common indication for the use of this procedure is detoxification of anuric animals suffering from primary renal failure. Peritoneal dialysis may also be used to remove xenobiotics, hydrate dehydrated animals, dehydrate over-hydrated individuals, or correct hypothermia if warmed dialysates are used. Peritoneal dialysis must be used repeatedly to be of much value. The technique should be learned before the emergency arises. Ion trapping the toxicant in the dialysate may be used where it will not aggravate acidosis or alkalosis.

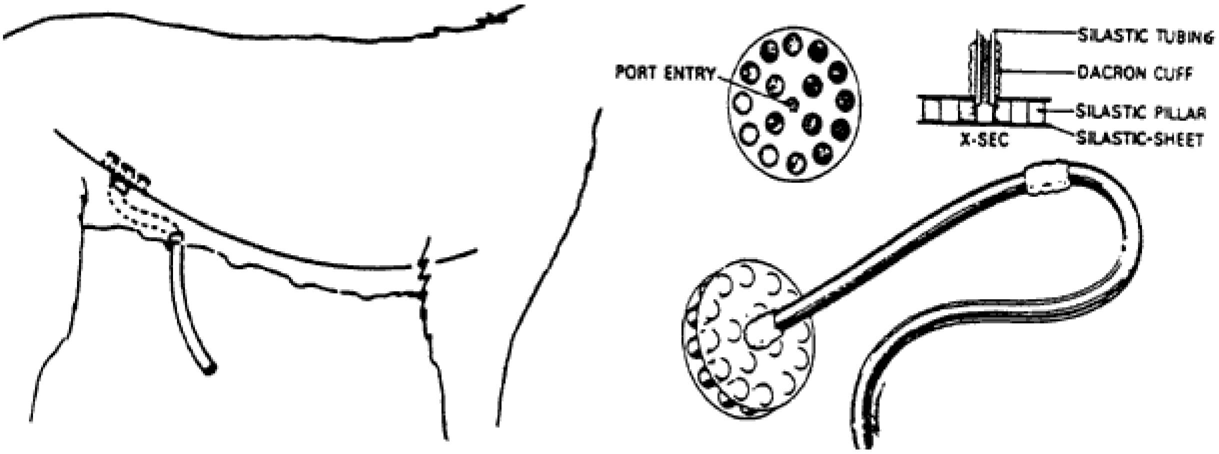
Bilaterally nephrectomized dogs have been kept alive for up to 111 days by peritoneal dialysis. The most serious complications are peritonitis and penetration of the abdominal viscera during insertion of the trochar or cannula. Attention must also be directed toward avoiding overhydration and loss of protein and electrolytes.

Peritoneal dialysis is sometimes the detoxification method of choice in small animal practice. These instances include situations in which: more conservative therapy is inadequate, whenever there is unresponsive anuria, and when there is progressive clinical deterioration in spite of treatment.

In order to rationally employ peritoneal dialysis as an aspect of therapeutic regimen, several aspects of the toxicant must also be considered. These include the facts that: **a**) the poison should diffuse through membranes at a reasonable rate; **b**) a significant quantity should be in the plasma water or rapidly equilibrate with it; **c**) the degree of toxicosis should be directly related to the blood concentration and duration of exposure to the poison; and **d**) the amount of poison dialyzed must significantly add to the normal mechanisms for disposal of the toxin under the physiological circumstances of the patient. Highest clearance rates can be achieved with small molecular weight molecules.

Technique for Peritoneal Dialysis - Dialysate--contains dextrose (1.5 - 4.25%) to induce osmotic fluid removal from the animal. Dialysate should be prewarmed. Commercially available dextrose dialysate bags are preferred (Dianeal 137 with 1.5% dextrose-viaflex).

A disc peritoneal dialysis catheter (Purdue column catheter) is placed into the lower abdominal quadrant. These are reported available from Henry Schein at (800) 537 - 2980. The disc is placed firmly against the parietal peritoneum and a routine closure of the abdomen performed with the catheter exiting through an adjacent stab incision.



Dialysate is instilled into the abdomen until mild abdominal distension is noted. Fluid is left in the abdomen for 45 - 50 minutes. Dialysis cycles may be repeated hourly until clinical improvement (or decreased uremia) occurs.Complications of peritoneal dialysis include peritonitis.

Peritoneal dialysis has been effectively utilized in human patients with barbiturate, ethylene glycol, lithium, theophylline, salicylate, and quinidine toxicosis. Other approaches which may eventually become more widely employed in veterinary medicine include **Hemodialysis** and hemoperfusion, using newer, less expensive, and even back-pack artificial kidneys. Hemodialysis was introduced experimentally in 1913 in an evaluation of the ability to remove salicylate from dog's blood. The first successful clinical experiences were reported in the mid 1950s in human patients with severe salicylate poisoning. Several hemodialysis techniques are available, including: **1**) aqueous hemodialysis (most commonly used for toxicoses), **2**) lipid hemodialysis, and **3**) ultrafiltration dialysis. The driving force in conventional hemodialysis is the concentration gradient of unbound ultrafilterable solute between the plasma and the dialysate employed. Hemodialysis equipment employs a blood delivery system, dialyzer, and dialysate.

Additionally, **Hemoperfusion** using activated charcoal, ion-exchange resins, or lipid aqueous phase columns may be used. **Hemoperfusion** was introduced in human clinical toxicology in 1965 for treatment of acute barbiturate toxicosis. During hemoperfusion, blood is pumped through an extracorporeal circuit containing a filtering cartridge. Cartridges may contain activated charcoal or resins (XAD-4) which will absorb the toxicant. Hemoperfusion has become the method of choice for the treatment of life-threatening human poisoning from a wide variety of toxicants and drugs.

The use of both hemoperfusion and hemodialysis do not replace more commonly employed methods of decreasing a toxicant's action. These techniques are, however, being employed (e.g., one study reported that approximately 0.15% of all overdose patients in the United States undergo hemodialysis or hemoperfusion) in some human hospitals. At the present times due to the expense and technical difficulties in performing these techniques, their use in animals is experimental.

f) Drug Antibodies

Attempts have been made to employ the use of specific FAb drug antibody fragments for the treatment of severe digoxin poisoning in man. FAb fragments bind to the specific drug (antigen) with high specificity and result in "neutralization." Immunopharmacological techniques are largely experimental at the present time; however, as clinical experience is gained with these methods, their use may increase in the future. Specific antibodies have been developed and found to be effective in experiments evaluating animals exposed to digitalis glycosides and the mycotoxin T-2 toxin. These techniques are already being used routinely in some human hospitals.

7. Use of Antidotes

Antidotes are best considered with individual toxicants and are not discussed herein. Some antidotal information on the labels of commercial products is out of date. When in doubt contact the National Animal Poison Control Center.

Section II: Toxicants that Affect the Nervous System

Overview of Toxicants that Affect Neurotransmitters

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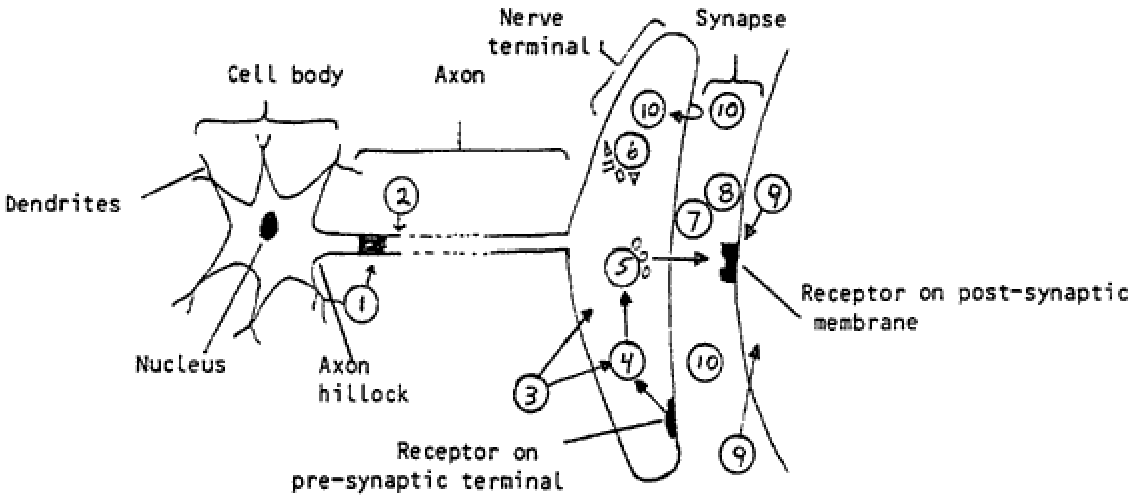
General

- Transmission of nervous impulses across the synapse is chemically mediated through neurotransmitters.
- Neurotransmitter is released from the presynaptic nerve terminal of a stimulated neuron, crosses the synaptic cleft, and combines with a specific receptor on the postsynaptic membrane. Binding to the postsynaptic receptor causes a conformational change in the postsynaptic membrane and, depending on the nature of the neurotransmitter and receptor, causes either depolarization (excitation) or hyperpolarization (inhibition) in the postsynaptic neuron.
- Criteria used to define neurotransmitters:
  - Substance must **be synthesized and stored** within the neuron from which it is released.
  - Substance is released from neuron on arrival of a nerve impulse.
  - A synthetic neurotransmitter applied exogenously must mimic the actions of the true neurotransmitter on the postsynaptic membrane.
  - A mechanism for the rapid termination of the action of a released neurotransmitter must exist.
- Classes of neurotransmitters:

  - Acetylcholine (ACh)
  - Catecholamines: dopamine (DA), norepinephrine (NE), epinephrine (E)
  - Amino acids and amino acid derivatives: Serotonin (5-hydroxytryptamine = 5-HT), gamma-aminobutyric acid (GABA), histamine, glycine, aspartic acid, glutamic acid
  - Peptides: enkephalins, thyroid-releasing hormone, substance P, bombesin, endorphins



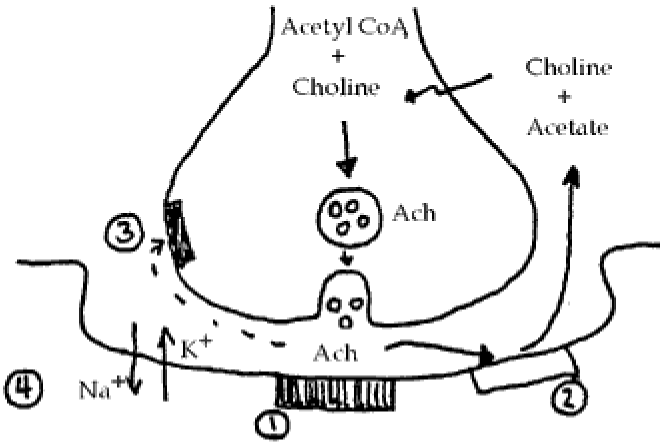
Sites at which toxins can act to modify neurotransmission
1) axonal transport, **2**) axonal membrane, **3**) precursor availability, **4**) neurotransmitter synthesis, **5**) storage, **6**) intra-cellular organelles, **7**) neurotransmitter release, **8**) receptor sites, **9**) postsynaptic mechanisms, **10**) neurotransmitter-inactivating mechanisms [1].

Acetylcholine

Synthesized from choline and acetyl CoA by choline acetyltransferase.

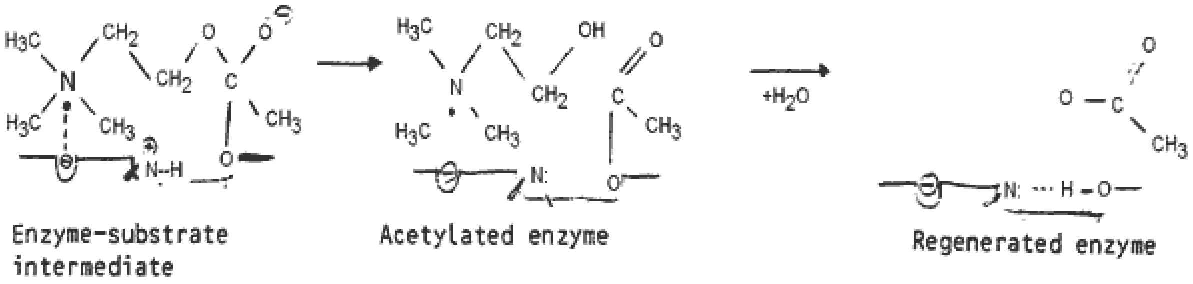
Choline	**Acetylcholine**
$(CH_3)_3N^+ -CH_2 -CH_2OH$ + acetyl CoA --->	$(CH_3)_3N-CH -CH_2 -O-C-CH_2$ + CoA

- Broken down by acetylcholinesterase to choline and acetate



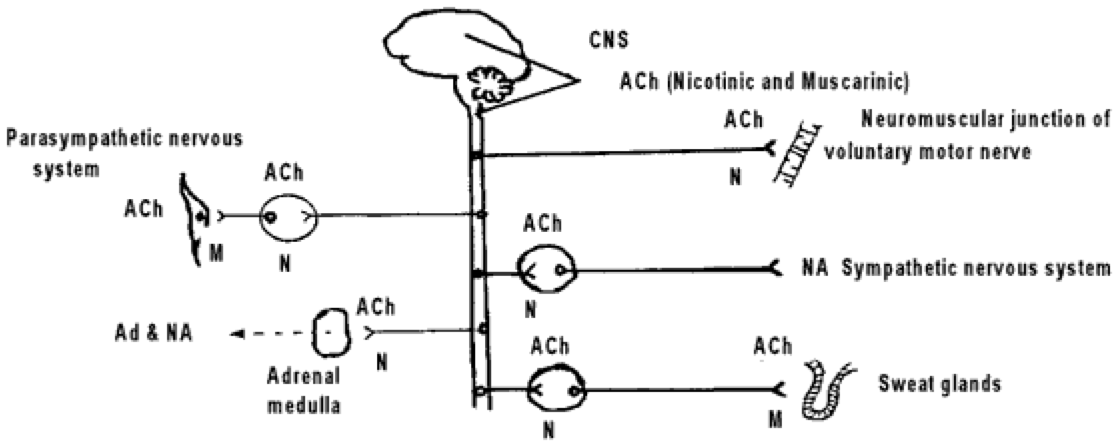
Schematic of cholinergic synapse:
1) Postsynaptic receptor.
2) Acetylcholinesterase.
3) Presynaptic cholinergic receptor.
4) Membrane change in permeability occurs post-ACh binding.

Acetylcholine **Choline** **Acetic Acid**



Action of acetylcholine and acetylcholinesterase

- Functions as neurotransmitter at following sites:
  - All preganglionic nerve terminals (both parasympathetic and sympathetic) of the autonomic nervous system.
  - All postganglionic parasympathetic nerve terminals.
  - The neuromuscular junction (voluntary nerve to skeletal muscle).
  - The adrenal medulla.
  - The central nervous system.
  - Postganglionic sympathetic nerve terminals at sweat glands.
- Two main types of cholinergic receptors:
  - Muscarinic receptors - mimic the effect of parasympathetic nerve stimulation (slow heart, miosis, exocrine gland stimulation, smooth muscle stimulation in the GI and bronchioles, micturition).
  - Nicotinic receptors - located at the neuromuscular junction of voluntary nerves and skeletal muscle, at all ganglia in the autonomic nervous system, at the adrenal medulla, and in the CNS.


CNS
ACh (Nicotinic and Muscarinic)
ACh
Neuromuscular junction of voluntary motor nerve
N
Parasympathetic nervous system
ACh
ACh
M
N
ACh
NA Sympathetic nervous system
N
ACh
Ad & NA
N
Adrenal medulla
ACh
ACh
Sweat glands
N
M

Location of cholinergic synapses in the nervous system - **N** = postsynaptic nicotinic receptors, **M** = postsynaptic muscarinic receptors, **Ad** = adrenaline release from adrenal medulla, **NA** = noradrenaline release from sympathetic nerve ending.

Table 1 - 1. Drugs and Toxicants Modifying Cholinergic Transmission

Toxicant	**Effect**
Hemicholinium	Block choline uptake with consequent depletion of ACh
4-Aminopyridine Black Widow spider venom Botulinum toxin	Increased release of ACh Explosive release of ACh Blocks release of ACh
Acetylcholine Muscarine Methacholine Carbachol Bethanechol Pilocarpine Arecoline (from areca nut)	Muscarinic receptor activation
Slaframine Muscarinic/histaminic mushrooms	Stimulates muscarinic receptor especially in exocrine glands
Atropine Benztropine Scopolamine Belladonna (*Atropa belladonna*) Henbane (*Hyoscyamus niger*) Jimson weeds (*Datura stramonium*) Tomato, etc.	Muscarinic receptor blocker
Acetylcholine Nicotine sulfate Tobacco (*Nicotiana*) Indian tobacco (*Lobelia*) Poison hemlock (*Conium maculatum*) Kentucky coffee tree (*Gymnocladus dioica*) Lupine (*Lupinus*) Mescal bean (*Sophora* spp.) Goldenchain (*Laburnum anagyroides*) Blue green algae - Anatoxin-A	Nicotinic-receptor activation
(+)-Tubocurarine Hexamethonium Gallamine Pancuronium Larkspur (*Delphinium*)	Nicotinic receptor blocker at neuromuscular junction
Organophosphate insecticides	Anticholinesterases

Carbamate insecticides Blue green algae - Anatoxin-A(s) *Solanum* spp. (significance of this mechanism is controversial in *solanum* and other Solanaceae) Black nightshade (*S. nigrum*) Potato (*S. tuberosum*) Horse nettle (*S. tuberosum*) European bittersweet (*S. dulcamara*) Jerusalem cherry (*S. pseudocapsicum*)	

Catecholamines

- Synthesized from tyrosine
- Broken down by monoamine oxidase (MAO) and catecholamine o-methyltransferase (COMT)

Norepinephrine

- Neurotransmitter in postganglionic sympathetic nerves (stress, fright, fight, or flight reaction) and within the central nervous system. Norepinephrine is also released in association with epinephrine from the adrenal medulla.
- Two main types of receptors:
    - α-adrenergic receptors:
        - α_1 adrenoreceptor--postsynaptic receptor on smooth muscles and glands.
        - α_2 adrenoreceptor--presynaptic receptor located on postganglionic neurons, mediating feedback inhibition of norepinephrine release. Postsynaptic a_2 receptors also appear to be present at extrasynaptic sites in the blood vessels and in the CNS.
    - β-adrenergic receptors:
        - β_1 adrenoreceptors - in heart.
        - β_2 adrenoreceptors--other tissues outside CNS.
- Functions of α-adrenoreceptors:
    - α1 receptors - mydriasis - contraction of radial muscle of iris.
    - α receptor - asoconstriction.
    - α_1 receptors - GI nonsphincteric smooth muscle relaxation; a receptors - sphincter muscle contraction.
    - α receptor--constriction of the trigone and sphincter in bladder.
    - α receptor--contract smooth muscle of pilomotor muscles, nictitating membrane, splenic capsule and salivary glands.
- Functions of β-adrenoreceptors:
    - β_1 receptors in heart--stimulation results in increase in both the force and rate of contraction.
    - β_2 receptors--vasodilation in skeletal muscles and liver.
    - β_2 receptors--relaxation of bronchial smooth muscle--bronchodilation.
    - β_2 receptors--relaxation of nonsphincteric smooth muscle of GI tract.
    - β_2 receptors--mediate relaxation of uterus in pregnancy--relaxation of detrusor muscle of bladder.
    - β_1 receptors--increased renin release from juxtaglomerular cells.
    - β_2 receptors--enhance glycogenolysis in liver, β_1 receptors increase lipolysis in adipose tissue, and decrease release of insulin from pancreas
    - Increase cAMP synthesis
        - cAMP alters membrane permeability to ions and changes intracellular ion binding.
        - cAMP is broken down by phosphodiesterases.
        - Substances inhibiting phosphodiesterases (methylxanthines) prolong the life of cAMP and tend to potentiate and prolong the effects of β -adrenoceptor stimulation.

Table 1 - 2. Drugs and Toxicants Modifying Noradrenergic Transmission

Mechanism	Drug	Effect
Synthesis	α-methyl-DOPA α-methyl-p-tyrosine Disulfiram (Antabuse®)	Synthesis of false transmitter Inhibits tyrosine hydroxylase Inhibits dopamine-β-hydroxylase
Storage	Reserpine Tetrabenazine	Disrupt norepinephrine (NE) storage
	MAO inhibitors	Enhance NE storage
Release	(+)-amphetamine Tyramine Ephedrine	Indirectly acting sympathomimetic amines, cause release of NE
	Guanethidine Debrisoquine Bethanidine Bretylium	Adrenergic neuron blockers, decrease NE release
Receptors	NE Phenylephrine (α1) α-methyl-NE Clonidine (α2)	α -adrenoceptor activation
	Phentolamine Phentoxybenzamine	α -adrenoceptor blockers
	NE Adrenaline Isoproterenol ($\beta_{1,2}$) Albuterol Terbutaline (β_2) Dobutamine (β_1)	β -adrenoceptor activation
	Propranolol (β_1,β_2) Metoprolol (β_1) Esmolol (β_1) Oxprenolol Sotalol Alprenolol	β -adrenoceptor blockers[1]
Postreceptor	Methylxanthines: Caffeine Theophylline Aminophylline	Phosphodiesterase inhibitors (minor site of action)
Inactivation of uptake	Cocaine Imipramine Amitriptyline	Neuronal-uptake inhibitors
of metabolism	Iproniazid Nialamide Phenelzine Tranylcypromine Pargyline	MAO inhibitors

See Ware [2], for a more comprehensive review of β blockers.

Dopamine

- Neurotransmitter in the CNS.

- Functions: integrates incoming sensory stimuli; initiates and controls fine movement (nigro-neostriatal pathway); controls emotional behavior (midbrain mesolimbic-forebrain system); controls hypothalamic-pituitary endocrine system (tubero-infundibular system).

Table 1 - 3. Drugs which Modify Dopaminergic Transmission

Mechanism	Drug	Effect
Synthesis	L-DOPA α-methyl-p-tyrosine Carbidopa Benserazide	Increased synthesis Inhibits tyrosine hydroxylase Inhibit DOPA decarboxylase outside CNS
Storage	Reserpine Tetrabenazine MAO inhibitors	Disrupt dopamine storage Enhance dopamine storage
Release	(+)-amphetamine Phenmetrazine Mazindol Tyramine	Increase release of dopamine
Receptors	Dopamine Apomorphine Bromocriptine ADTN Piribedil	Dopamine-receptor activation
	Chlorpromazine Fluphenazine Haloperidol Pimozide Metoclopramide	Dopamine-receptor blockers
Postreceptor	Methylxanthines: Caffeine Theophylline Theobromine	Phosphodiesterase inhibitors
Inactivation of Uptake	Amphetamines Nomifensine Benztropine Benzhexol Mazindol	Neuronal dopamine uptake inhibitors
of metabolism	Iproniazid Tranylcypromine Phenelzine	MAO inhibitors

Amino Acid Derivatives
Serotonin (5-HT) -

- Located peripherally in enterochromaffin granules of the gut and in blood platelets; it has a neurotransmitter role only in the CNS.
- Has the structure of an indole alkyl amine and is synthesized from the amino acid L-tryptophan.
- Distribution of 5-HT in the CNS forms a diffuse network, and exact functional roles are not firmly established.
- May be important in the control of mood and behavior, motor activity and its control, feeding and control of hunger, thermoregulation, sleep, certain hallucinatory states, and possibly some neuroendocrine control mechanisms in the hypothalamus.

Table 1 - 4. Drugs which Modify 5-Hydroxytryptaminergic Transmission

Mechanism	Drug	Effect
Synthesis	L-tryptophan	Increases synthesis
	p-chlorophenylalanine	Inhibits tryptophan hydroxylase
Storage	Reserpine Tetrabenazine	Disrupt 5-HT storage
	MAO inhibitors	Enhance 5-HT storage
Release	Fenfluramine Chlorphentermine Amphetamines	Release 5-HT onto receptors
Receptors	5-HT LSD DMT Quipazine	Activate 5-HT-receptor
	Cyproheptadine Methysergide Mianserin	Block 5-HT-receptor
Inactivation of uptake	Tricyclic antidepressants Mianserin Fenfluramine	Inhibit neuronal 5-HT uptake
of metabolism	Phenelzine Iproniazid Tranylcypromine	Inhibit MAO

Histamine

- Occurs in several tissues of the body - stored in a bound form in mast cells, platelets, and basophils and released in response to stimuli such as allergic reactions and injury. In the CNS, gastric mucosa, lungs, and skin, histamine is stored in a different complex, and at these sites, it can be released in response to signals of hormonal or neuronal origin.
- Formed by the decarboxylation of L-histidine.
- Two types of histamine receptors peripherally:
  - H_1 receptors - bronchoconstriction, increased capillary permeability, wheal and flare reaction.
  - H_2 receptors- gastric acid secretion.
- Uneven distribution of histamine receptors within CNS--suggested that histamine may have a role in arousal, in mechanisms related to nausea and vomiting, and in the control of blood pressure and water metabolism.

Table 1 - 5. Drugs which Modify Histaminergic Mechanisms

Mechanism	Drug	Effect
Synthesis	-	-
Storage	-	-
Release	Injury (+)-tubocurarine Morphine Dextran	Release histamine onto receptors
	Cromolyn sodium	Inhibits histamine release
Receptors	Histamine	Activate H_1-histamine-receptor

	2-methyl histamine Mepyramine Promethazine Chlorpheniramine Histamine Betazole Cimetidine Burimamide Metiamide Ranitidine	Block H_1-histamine-receptor H_2-histamine-receptor activation H_2-histamine-receptor blockers
Inactivation	-	-

Amino Acid Neurotransmitters

- Certain amino acids found within the mammalian CNS appear to fulfill the criteria for neurotransmitters. Amino acids found in peripheral nervous system don't fulfill all the criteria.
- Two main classes:
    - Excitatory - acidic amino acids-glutamic acid, aspartic acid.
    - Inhibitory - neutral amino acids-q-aminobutyric acid (GABA), glycine, taurine.
- Excitatory amino acid neurotransmitters cause increased sodium conductance of the postsynaptic membrane and increase neuronal firing rate (like acetylcholine).
- Inhibitory (or depressant) amino acid neurotransmitters cause increased chloride conductance of postsynaptic membranes and decreased firing rate.

Gamma-Aminobutyric Acid

- Inhibitory neurotransmitter in brain, spinal cord, and retina.
- Formed by the decarboxylation of L-glutamic acid.
- Widespread distribution within CNS, with high concentrations in the hypothalamus, hippocampus, and basal ganglia of the brain in the substantia gelatinosa of the dorsal horn of the spinal cord. Most GABA is associated with short inhibitory interneurons, although some long-axon pathways within the brain are known.
- Presynaptic inhibition--reduces excitatory transmission in primary afferent fibers by action of GABA.
- If GABA function is impaired, may result in convulsive, tetanic, and spastic disorders.

Table 1 - 6. Drugs and Toxicants which Modify GABA Transmission

Mechanism	Drug	Effect
Synthesis	Allylglycine 3-mercaptopropionic acid	Inhibit glutamic acid decarboxylase
Storage	-	-
Release	Ivermectin	Increases release of GABA
Receptors	GABA Muscimol Ivermectin Benzodiazepines Barbiturates Ivermectin Piperazine Bicuculline Picrotoxin Benzylpenicillin α CN-pyrethroids	Activates GABA receptors Enhance GABA-receptor activity Block GABA receptors

	Cyclodiene organochlorine insecticides	
Inactivation of uptake of metabolism	β-alanine Nipecotic acid Ethanolamine-O-sulphate Sodium valproate	Inhibit GABA uptake Inhibit GABA transaminase (GABA-T)

Glycine

- An important inhibitory neurotransmitter in small inhibitory interneurons in the brainstem and spinal cord.
- Effects of glycine are postsynaptic.
- Neurotransmitter for Renshaw cells in ventral horn of spinal cord--Renshaw cells receive excitatory input from recurrent collaterals of spinal motor neurons--axons from the Renshaw cells synapse on the motor neuron.
- Probably involved in regulation of spinal and brainstem reflexes.

Table 1 - 7. Toxicants Affecting Glycine Neurotransmission

Toxicant	Mechanism of Effect
Tetanus toxin	Inhibits release of glycine
Strychnine Brucine *Gelsemium* *Calycanthus*	Block glycine receptors
Penitrem A (tremorgenic mycotoxin)	Competitively inhibits glycine and GABA at receptors

Adenosine

- Inhibitory neurotransmitter in the brain.
- Inhibition by methylxanthines, especially caffeine, results in increased alertness.

L-Glutamic Acid

- Excitatory neurotransmitter.
- In spinal cord concentrated at primary afferent fibers in dorsal roots--may relay sensory information and regulate motor activity and spinal reflexes.
- In brain--high concentrations in cortex, hippocampus, neostriatum, and cerebellum.
- Role not determined yet.
- Some excitatory amino acids found in certain toxic plants over-stimulate glycine receptors. Persistent overstimulation can lead to neuronal damage.

L-Aspartic Acid

- Excitatory neurotransmitter.
- Highest concentration in midbrain and dorsal and ventral grey matter of spinal cord.
- Role unknown.

Taurine

- Inhibitory neurotransmitter or neuromodulator.
- May act as a membrane stabilizer.
- Functional role unknown.

Peptides

- Relatively newly recognized--still unsure if true neurotransmitters or neuromodulators.

Endorphins and Enkephalins

- Mimic effects of morphine in biological system.

Substance P

- Concentrated in dorsal horn of spinal cord and substantia nigra of brain.

Toxicants Associated with Seizures

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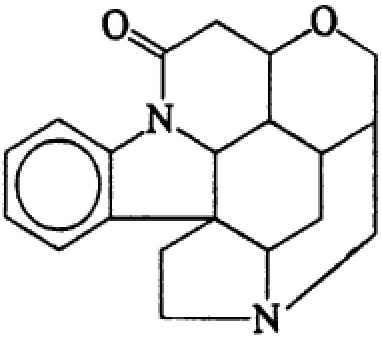
Strychnine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
All, esp.dogs	Minutes to Hours	Hours to few days	

Sources

- Strychnine is a bitter tasting alkaloid extracted from the seeds of an Indian tree, *Strychnos-nux vomica*.
- Present in "*Nux Vomica*" medications and homeopathic preparations.
- Supposed ruminatoric but is ineffective. Not a ruminatoric. There is no logical therapeutic use.
- Present in pesticides to control:
  - Gophers, moles (subsoil use) - Most products, especially those available OTC.
  - Rats.
  - Coyotes (not leagal in the USA).
  - Infrequently relay toxicosis; may be more of a problem in raptors (Redig et al., 1982).
- Often dyed - red or green.
- Restricted in some states more than others.
- OTC availability - 0.5% (or 0.3%) or lower concentrations for subsoil use in the United States.
- All species are sensitive; problems mainly occur in small animals, especially dogs.
- Both accidental and malicious poisonings occur.

Strychnine



Toxicity

- Approximate lethal doses. (Primarily from Kirk's Current Veterinary Therapy, Volume VIII, p. 98. - Available from amazon.com -).
  - Bovine 0.5 mg/kg
  - Equine 0.5 - 1.0 mg/kg
  - Porcine 0.5 - 1.0 mg/kg.
  - Canine 0.75 mg/kg.
  - Feline 2.0 mg/kg.
  - Rat 3.0 mg/kg.
  - Fowl 5.0 mg/kg.
  - Mallard ducklings 2 mg/kg.
  - Pheasants 24.7 mg/kg.

    - Thus based on 0.3% bait, 3 grams of bait would be potentially fatal to a 12 kg dog.
    - Steep dose-response curve so that any animal displaying clinical signs must be carefully attended.

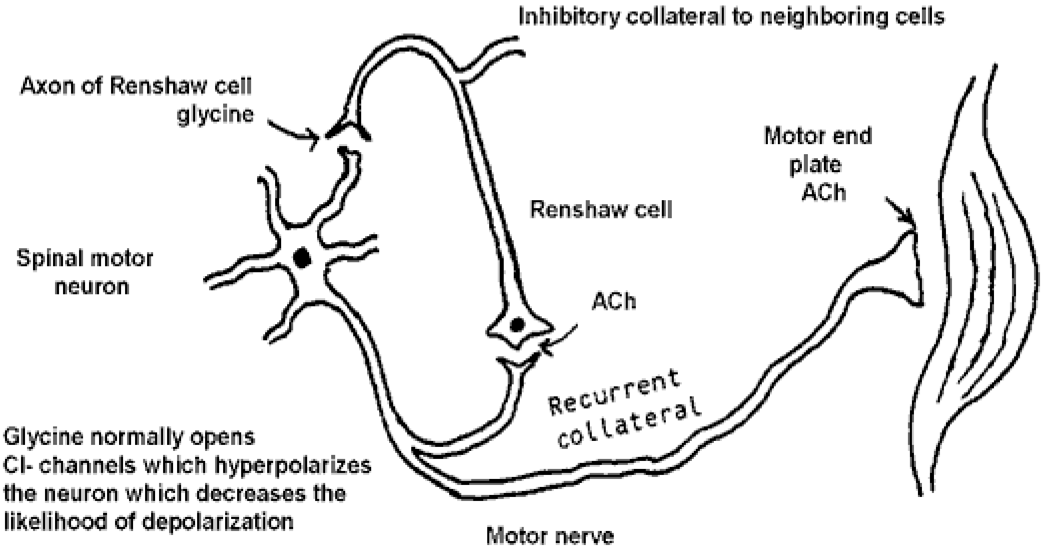
Absorption, Distribution, Metabolism and Excretion (ADME)

- Ionized in acid medium ($pk_1 = 6.0$, $pk_2 = 11.7$) and therefore absorbed in small intestine, but absorption is rapid.
- Metabolism of parent compound in liver; metabolites excreted in urine.
- Highest tissue concentrations occur in blood, liver, and kidney. Does not concentrate in nervous tissues. At death, the highest concentrations are usually present in stomach contents.

Mechanism of Action

- Strychnine acts by competitively and reversibly antagonizing the inhibitory neurotransmitter glycine at postsynaptic neuronal sites in the spinal cord and medulla.
- Result is unchecked reflex stimulation, with predominance of more powerful extensors which results in rigidity.

Strychnine Competes with Glycine


Inhibitory collateral to neighboring cells
Axon of Renshaw cell glycine
Motor end plate ACh
Renshaw cell
Spinal motor neuron
ACh
Recurrent collateral
Glycine normally opens Cl- channels which hyperpolarizes the neuron which decreases the likelihood of depolarization
Motor nerve

Signs

- Onset: 10 to 120 minutes after ingestion.
- Even sublethal doses may cause elevated blood pressure and heart rate.
- Usually no vomiting.
- Anxiety, stiffness.
- Violent tetanic seizures.
    - Spontaneous or initiated by numerous stimuli, which is a diagnostic feature, however it can be hazardous (and lethal) to deliberately initiate such seizures. Initiation of seizures is therefore contraindicated.
- Saw-horse stance.
- Opisthotonus and persistent rigid extension of all four limbs.
- Generally, there are no paddling and no running movements, masticatory activity, or salivation.
- Facial musculature contraction causes strained expression.
- Rigidity inhibits respiration, apnea results.
- Periods of relaxation gradually become fewer and shorter.
- Rarely loss of consciousness.

- Death from anoxia and exhaustion.
- Myoglobinuria possible.

Lesions

- Rapid rigor, rapid relaxation.
- Cyanosis, possible traumatic evidence of seizures.
- Birds that died (dunlin and killdeer) exhibited an unusual posture with the wings folded over their back, straightened toes, with their bill in the soil and excreta extruded from their vent.

Diagnosis

- Food or bait usually in stomach if recently exposed.
    - Analysis of:
        - Baits.
        - Frozen stomach contents obtained by lavage or at necropsy in lethal cases are most useful.
        - Frozen liver.
        - Frozen urine. Urine is the primary route of elimination but some animals may die too fast to detect strychnine in the urine.
- Histopathology on brain should reveal normal tissue or perhaps changes consistent hypoxia.

Treatment

- Primary goal - prevent asphyxia.
- Pentobarbital - the preferred drug for relaxation; given to effect with care. It is essential to be ready to intubate and administer artificial ventilation in severely affected animals.
- Robaxin (methocarbamol) at 150 mg/kg, IV, repeat doses of 90 mg/kg as needed has been recommended by some authors. NOTE: unnecessary when using pentobarbital.
- Inhalation anesthetics.
    - May have to maintain in anesthetized state up to 48 hours.
    - Contraindicated:
        - Ketamine - due to motor stimulatory effects.
        - Morphine - due to respiratory depression, possible stimulation of spinal cord.
- Artificial respiration if hypoxic.
- Detoxification - can shorten course - lessen severity.
    - Emetics are generally contraindicated due to the risk of initiation of a seizure and aspiration.
    - Enterogastric lavage.
        - Activated charcoal and a saline or osmotic cathartic.
    - Fluids, forced diuresis with 5% mannitol in 0.9% normal saline at 7 mg/kg/hour.
    - Ammonium chloride (100 mg/kg, BID, po) to acidify urine thereby increasing protonation of strychnine to reduce its reabsorption across the renal tubular membrane. NOTE: Ammonium chloride is infrequently needed and is **contraindicated** if the animal is acidotic from exertion or from respiratory failure due to tetany of the muscles of respiration or when myoglobinuria is present.
    - If the animal has a severe metabolic acidosis, the slow infusion of fluids with added bicarbonate is indicated. If acidosis is of respiratory origin, administration of bicarbonate is inappropriate.
    - Experimentally, Sargiah (1985) found that diazepam, glycine, and beta-alanine given IP raised the seizure threshold in mice. However, in another report, glycine given to mice in high doses (1 - 6 g/kg, IP) caused hypothermia and sedation but was incapable of preventing strychnine convulsions (Lapin, 1981). Further evaluation of glycine and other amino acids is required before they can be recommended.
    - Cardiovascular effects, if they occur, can be abolished by combinations of alpha- and beta-adrenergic blocking agents and can be reduced significantly by diazepam. Specific therapy depends on EKG and clinical signs.
- Care must be taken with any manipulation of the patient due to the excessive muscle stimulation and reflex rigidity that may readily occur.

Key Features

- Baits, malicious poisoning.
- Strychnine in stomach contents.
- Interferes with glycine at postsynaptic neuronal sites in spinal cord.
- Tetanic seizures, asphyxia, opisthotonus, rapid onset and progression in most cases.
- Pentobarbital or other anticonvulsant treatment combined with detoxification using activated charcoal and (sometimes) acidification of the urine while avoiding contraindicated drugs.

Calycanthus - Bubby Bush

Calycanthus - *C. fertilis* (Problem plant, a wild shrub); *C. floridus* (Ornamental plant)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
Herbivores, esp. cattle	Minutes to Hours	Few days; often lethal	

Common Names

- Carolina allspice
- "Bubby" bush
- Sweet shrub
- Hairy allspice
- Pale sweet shrub
- Smooth allspice
- Strawberry bush
- Indian toothpick

Description

Height: 6 - 10 feet; circumference 6 - 12 feet; summer foliage dark green, fall foliage is yellow.
Leaves alternate, 2 1/2 inches, somewhat rough above, generally egg-shaped with blunt or pointed tips.
Flowers brown - maroon and fragrance suggesting strawberries.
Fruit is like a rose hip.
Seed pods, brownish, urn-shaped receptacle containing many 1-seeded brown achenes. In some species, stems are pubescent; in others, they are hairless.
Pest resistant. Bark has been used as a subsitute for cinnamon.

Distribution

Most reports of poisoning are apparently from Tennessee. Also reported in bulletins from Georgia, North Carolina, and Alabama.

Toxic Principle

Calycanthine, an indole alkaloid found in the seeds, with a pathophysiological action similar to strychnine.

Signs

- Unexpected deaths.
- Cows laying on side with severe tetanic spasms.
- Muscle fasciculations.

- Injected sclera, pupillary dilation.
- When touched, the animals develop rigid extension, opisthotonus, and convulsions.
- Respiratory rates elevated, such as 100 and 108.
- Urinalysis, CBC, and routine blood chemistry panels within normal limits.
- May seize while standing in the field.
- Rapid death.

Lesions

No lesions, but in rumen can find seed pods (husks) and seeds typical of the *Calycanthus* shrub.

Diagnosis

- The leaves may be undisturbed, but there may be no seed pods present, presumably indicating that they had been eaten.
- Presence of *Calycanthus* seeds in the rumen contents.
- Tentative diagnosis made using the history, signs, evidence of consumption of the shrub (seeds) and the lack of any other CNS stimulant or other explanation.

Treatment

- A successful approach used on bovine animals was comprised of a quiet stall, mineral oil orally, and thiamine, given intravenously the first day and then intramuscularly. Calves responded well and were released after 3 days. The remaining calves on pasture responded to no therapy and made an uneventful recovery.
- Based on extrapolation from strychnine toxicosis, repeated administration of activated charcoal, minimal stimulation and sedation with chloral hydrate (50 - 70 mg/kg, IV, to effect) or pentobarbital (30 mg/kg, IV, to effect) may be appropriate in ruminants. Prolonged anesthesia would generally be impractical in most ruminant cases.

Comment

There are numerous references citing the *Calycanthus* Shrub as being "thought to be toxic or dangerous, but rarely eaten". Nearly all references are directed to Dr. Chestnut's work in 1898 when, in his "Summary of Toxic Plants", he mentioned some unconfirmed poisonings in Tennessee. The older livestock owners in the Tennessee mountains and the Plateau area have long recognized the shrub as poisonous and have called it "Bubby".

Gelsemium - Yellow or Carolina Jessamine

Gelsemium sempervirens - Yellow jessamine, false jessamine; Trumpetflower, Carolina jessamine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
Herbivores, fowl	Minutes to several days	Few days; often lethal	

Description

Twining or trailing plant, evergreen, woody perennial. Ten to 20 ft in length. Adult plant may have stem up to 1 inch in diameter; younger stems are red-brown, wiry and tangled; very highly branched. Leaves are opposite, simple, glossy and short petioled, 2 - 4 inches long. Flowers in late winter or early spring; short axillary clusters; yellow, fragrant and funnel shaped.

Habitat

Virginia to Florida, Texas, and Central America. Coastal plain and lower piedmont from Virginia to Texas. In low ground and thickets of mountains, fencerows, woods, and fields; usually climbing on trees. Also used to cover porches and trellises.

Toxic Principle

Alkaloids of indole configuration, related to strychnine: gelsemine and gelseminine.

Toxicity

- Among the 10 poisonous plants which cause the most problems in North Carolina.
- Flowers, leaves, roots, and nectar are poisonous, also cause dermatitis.
- Honey from flowers may also be toxic.
- Rootstock and nectar most toxic.
- Livestock losses occur in winter when shortage of other forage exists.

Susceptible Species

Cattle, sheep, goats, horses, fowl, humans.

Signs

- Livestock on range often found in prostrate condition.
- Die within 24 - 48 hours after going down.
- Intense abdominal cramps.
- Muscle weakness.
- Convulsive movements of head, front legs, and sometimes rear legs.
- Slow respiration.
- Hypothermia.

Diagnosis

- Death due to respiratory paralysis.
- Fowl fed green leaves died in 5 - 11 days.

Lesions

Nonspecific.

Treatment

Terminate exposure, activated charcoal and saline cathartic; symptomatic and supportive care.

Tetanus

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
All species, esp. horses	Days to weeks	Days to months; potentially lethal	

Sources

- Tetanus toxin is produced by *Clostridium tetani* a gram-positive, spore-forming bacillus under anaerobic conditions.
- *C. tetani* spores are also commonly present in the feces of domestic animals, especially those of horses, and in soil contaminated by the feces.
- *C. tetani* spores may persist in soil for many years and are resistant to many standard disinfection processes, including steam heat (100º C for 15 minutes).
- Poisoning is known to result from clostridial growth in contaminated wounds in which anaerobic conditions predominate. The usual incubation period is 1 - 3 weeks. It is possible for the original point of entry to heal without any evidence of infection and for subsequent trauma, even months later to set up the necessary environment for clostridial growth and toxin production.

- Animals given appropriate preventative measures (toxoid and antitoxin) are at low risk of developing tetanus.
- The usual portal of entry in horses is deep puncture wounds. Clinical toxicosis is most likely when there is sufficient accompanying tissue damage to result in an anaerobic environment favorable to clostridial growth. Umbilical infections also occur in foals that receive no maternal immunity.
- The usual portal of entry in cattle is via the reproductive tract at parturition. Outbreaks of tetanus in cattle have suggested that the toxin may have been produced in the gut or ingested preformed in the feed. Grazing of rough, fibrous feeds before such outbreaks is a common factor in the history, and it is possible that infection may have begun via wounds in the oral cavity. Castrating and dehorning with elastic bands can also result in clostridial infection.
- In pigs, castration wounds are the most common point of infection.
- In lambs and adult sheep, infection is most often associated with castration, docking, or shearing. Docking with elastic bands is one of the most common causes of tetanus in lambs.

Mechanism

- Three exotoxins are produced by the vegetative form of *C. tetani*: tetanospasmin (causes clinical signs); tetanolysin (increases local tissue necrosis); and nonspasmogenic toxin (importance unknown).
- Tetanus toxin (tetanospasmin) is a protein (2 polypeptide fragments; total MW approximately 150,000). Transport to the CNS occurs retrograde within nerves and via the **bloodstream**. The course of axons in tissues can be traced, in a research setting, by applying a nontoxic fragment of tetanus toxin to a nerve terminal and, after allowing time for retrograde transport, staining tissue sections with an immunological probe for the toxin fragment. The toxin binds to gangliosides in the brain stem or spinal cord. It blocks inhibitory synaptic input, especially at glycine mediated sites, **by binding to the presynaptic membrane and blocking the release of glycine**, resulting in spastic paralysis. It may also inhibit release of GABA and other amino acid neurotransmitters.
- Tetanus toxin may also cause paralysis by inhibiting the release of acetyl choline at neuromuscular junctions (probably less important than inhibitory effect on release of glycine).
- Constant muscular spasticity may be produced and normally innocuous stimuli cause exaggerated responses.
- Death occurs as a result of rigidity of the muscles of respiration and associated asphyxia.
- Tetanus toxin may also cause "cardiovascular symptoms in patients whose spastic paralysis was controlled".
- Nonspasmogenic toxin is poorly understood and is thought to cause paralysis of the peripheral nervous system.
- Tetanolysin is antiphagocytic and enhances local tissue necrosis.

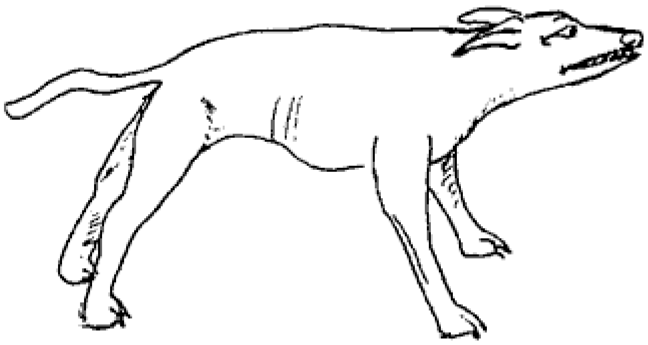
Susceptible Species

- Although all species of domestic animals are susceptible to tetanus, most cases appear to occur in the horse.
- Horses are the domestic species most sensitive to tetanus toxin.
- Pigs, cattle and sheep are less sensitive and dogs and cats are fairly resistant but are sometimes affected. Poultry are more resistant.
- Generally, tetanus occurs in individual animals although outbreaks have been described in cattle, young pigs, and lambs.

Signs

- Tetany, the predominant clinical sign of tetanus, is characterized by sustained tonic contractions of muscle without twitching.
- Incubation period varies from days to months. Infrequently the incubation period can be long, and in those cases, diagnosis may be difficult.
- Signs are referable to hyperesthesia, tetany and convulsions with eventual rigidity of the muscles of respiration, asphyxia, and death.
- Clinical signs may include a sawhorse stance, protrusion of the third eyelid, rigidity of the generalized musculature, "sardonic grin", and secondary postural effects which diminish defecation and urination. Rigidity with extension of the tail has been described for cats "pump-handle tail".
- Opisthotonus and persistent rigid extension of all four limbs.

- Stiff gait.
- Horses, spasms of the masseter muscles occur early in the disease, "lockjaw" results.
- If paralysis of laryngeal and pharyngeal musculature occurs, aspiration pneumonia may develop.
- Excitation or loud noises may elicit convulsions in hyperesthetic animals.
- Excess stimulation of sympathetic nervous system can occur with sweating, tachycardia, arrhythmias, vasoconstriction, colic.
- Complications due to recumbency occur, e.g., pressure induced neuropathy, decubital ulcers.
- As the dose of toxin is increased, paralysis can result.
- Localized tetanus involving only the muscle groups closest to the site of injury is relatively uncommon.



Characteristic "sawhorse" stance of a dog with generalized tetanus showing stiff, outstretched tail and contracted facial musculature.</P>

Lesions

- The only lesions which assist in the diagnosis of tetanus are the finding of appropriate wounds. Culture of the organism may be attempted.
- CSF normal.

Differential Diagnosis and Diagnosis

- Hypomagnesemia encephalitis, eclampsia, strychnine toxicosis.
- Culture is often unrewarding.
- EMG - normal nerve conduction velocities, persistent electrical discharges occur.

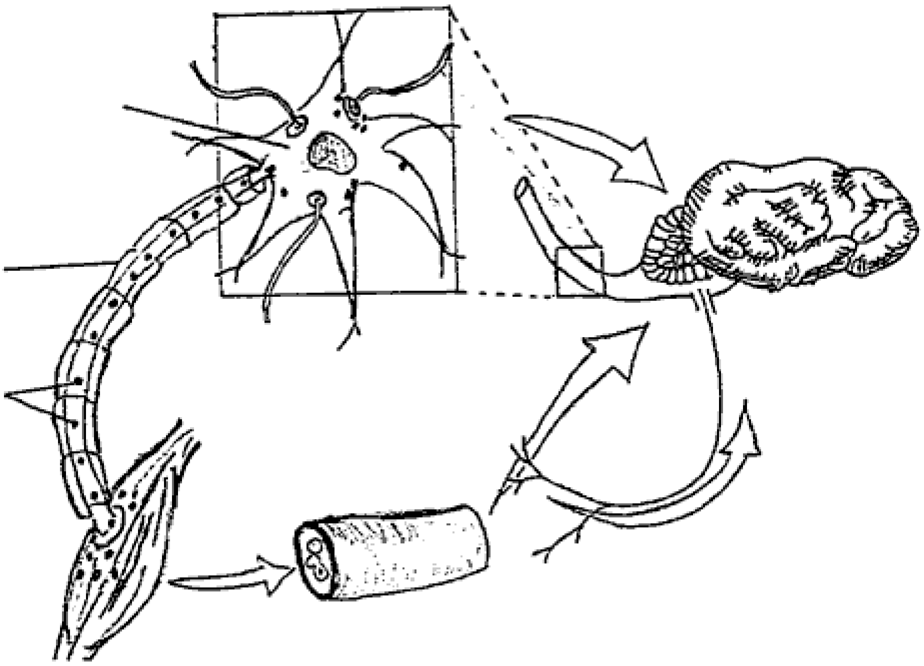
Treatment

- Keep animal in dark quiet room.
- Offending wound should be located and meticulously debrided.
- IV antitoxin [only after a test dose (SQ) to check for hypersensitivity reactions] will reduce uptake of toxin by nerves.
- Administration of tetanus antitoxin will not reverse the clinical signs.
- Suggested dosages of antitoxin range from 10 - 220 IU/kg. Probably 5,000 - 10,000 IU given IV or IM in an adult horse is adequate.
- Tetanus toxoid is administered concurrently.
- Local infiltration of wounds with antitoxin has been recommended (Blood, Henderson).
- Intrathecal administration of antitoxin has been described in humans and horses (Muylle et al.). Controversial. Greatest benefits early in disease course.
- Antibiotics (e.g., penicillin) are used to decrease bacterial numbers.
- Muscle relaxants most often used include guaifenesin guiacolate (5% to effect, keep standing), methocarbamol (10 - 20 mg/kg, q8h), and diazepam (0.05 - 0.4 mg/kg).
- Tranquilizers may be required. Promazine (0.5 - 1.0 mg/kg, IM) may provide 4 - 8 hours of relaxation.

Prognosis

- Many animals become dysphagic which necessitates intensive support measures.

- If animal is recumbent, generally the prognosis is poor. There is presently a 50% mortality rate for horses displaying neurologic signs at presentation.



Potential route of spread of tetanus toxin into the CNS. Figures from Greene ibid.

Key Features

- *Clostridium tetani* anaerobically produces toxin in wounds and umbilical tissues.
- Transfer to CNS via nerves and/or blood.
- Inhibition of release of glycine.
- Rigidity, tetany, debilitation.
- Therapy: antitoxin, antibiotics, sedation, support.
- Prevention: toxoid, antitoxin, good wound management, colostrum, antitoxin for foals.

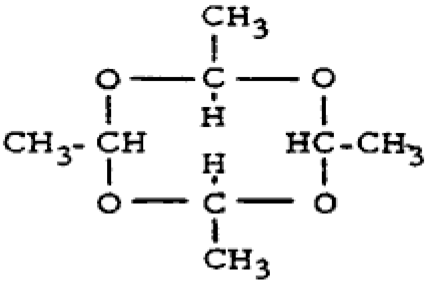
Metaldehyde

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
All species, esp. dogs	• Minutes to hours (neurologic or respiratory effects). • Days (liver failure).	• One to two days; often lethal • Days to months; liver failure rare.	

Sources

- Molluscicide - slug and snail baits - polymer of acetaldehyde. Occasional baits contains cereals: increases palatability.
    - Pellets. Snarol, Buggetta.
    - Liquid. Dead-line (sticky liquid).
    - Bait usually 3.5% metaldehyde.

    - Some products contain arsenic or carbamate (insecticidal compounds) which are usually of less toxicologic importance than the metaldehyde present.
    - Poisoning - coastal areas and south (especially in California).
- Used as a fuel in small heaters.
- Incidence in the early 1970's in California:
    - 4.5 cases/month/small animal practice - Sacramento area.
    - Some emergency clinics averaged 20 - 30 cases/week.



Structure of Metaldehyde

Susceptible Species

Dogs, cats, sheep, humans, others.

Toxicity

- Toxic oral dose of metaldehyde for most species is from 60 - 500 mg/kg.
- Minimum oral lethal dose metaldehyde.
    - Dog: 100 mg/kg.
    - Horse: 60 - 360 mg/kg.
    - Cow: 200 mg/kg.
- Reported LD_{50}
    - Dog: LD_{50} oral: 100 - 1000 mg/kg.
    - Cat: LD_{50} oral: 207 mg/kg.
    - Guinea pig: LD_{50} oral: 175 mg/kg.
    - Mouse: LD_{50} oral: 200 mg/kg.
    - Rat: LD_{50} oral: 227 mg/kg.
    - Rabbit: LD_{50} oral: 290 mg/kg.
- 3 - 4 ounces of most pelleted baits would be toxic to average size dog, sheep.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Acetaldehyde liberated by gastric hydrolysis of metaldehyde.
- Acetaldehyde - milder odor than formaldehyde.

Mechanism of Action

- Precise mechanism of action in mammals unknown.
- Acidosis presumably results from the subsequent metabolism of acetaldehyde and from other effects (tremors, seizures, exertion).
- Acetaldehyde may or may not directly cause the problems occurring in metaldehyde toxicosis.
    - Acetaldehyde not detected in tissue or serum from metaldehyde poisoned dogs.
- Brain concentration of 5-HT (5-hydroxytryptamine = serotonin) and noradrenaline are often inversely related to the prevalence of seizures.
    - A decrease in brain 5-HT and noradrenalin occurs in metaldehyde-poisoned animals.
    - Intraperitoneal administration of acetaldehyde to mice did not result in significant depression of 5-HT.

- An increase in monoamine oxidase (MAO) activity occurs during metaldehyde toxicosis in mice. However, MAO activity was unrelated to survivability of mice in this study. Conversely, MAO activity is decreased in acetaldehyde-poisoned mice.
- Decreases in the important inhibitory neurotransmitter gamma amino butyric acid (GABA) also occur in metaldehyde poisoned animals (mice). As GABA levels decreased so did survival rates.

Signs

- **Cattle**
  - Salivation, ataxia, hyperpnea, tremors, convulsions (convulsions may start at posterior end and progress forward). These may pitch cattle forward on their muzzles if severe. Frothy diarrhea sometimes occurs. Cyanosis. Loss of "blink" reflex and blindness. May overreact to external stimuli.
- **Sheep and Goats**
  - "CNS signs tremors fore and hind limbs, ataxia, convulsions, nystagmus, cyanosis, liver damage (pale and friable) in goats and sheep.
  - Uncommon cause of poisoning.
- **Horses**
  - Colic.
  - Mild leg tremors, hyperesthesia, diarrhea, sweating, hyperpnea (severely fluted nostrils).
  - Tachycardia, clonic spasms, incoordination, extended head, convulsive spasms.
  - Violent muscle spasms and ventroflexion of the spinal column just before death.
- **Dogs**
  - Often eat all the snail bait available to them.
  - Onset of signs - almost immediate up to 3 hours.
  - Sequence:
    - Increased heart rate, anxiety, nystagmus.
    - Mydriasis, hyperpnea, panting, hypersalivation (may be frothy) stiff legs, ataxia.
    - May be rapidly followed by muscle tremors, then vomiting, hyperesthesia, continuous convulsions, cyanosis, acidosis, diarrhea, dehydration, hyperthermia (to 108º F).
    - Convulsions more continuous than in strychnine poisoning. Also, external stimuli do not have the marked effect as seen in strychnine toxicosis.
    - Later stages may have depression followed by narcosis.
  - If death occurs, it is usually from respiratory failure and takes place from 4 - 24 hours after exposure. If animal survives this period, it may succumb to liver failure within 2 to 3 days.
  - Possible to have temporary blindness (which may last weeks) with normal pupillary reflexes.
- **Feline** (toxicosis not reported frequently):
  - Similar to canine except nystagmus may be more prevalent.
  - Depression, dyspnea, convulsions, tachycardia.
- **Birds**
  - Poisoning reported in ducks and geese.
  - Lethal dose ducks 300 mg/kg.
  - Signs include ataxia, opisthostonus, dyspnea, polypnea, tremors.

Lesions

- **Cattle**
  - Blood may fail to clot.
  - Dark, congested lungs.
  - Petechia in airways, throughout body.
  - Sometimes enteritis and massive endocardial hemorrhages.
- **Horse**
  - Lesions not diagnostic (not sufficiently specific).
  - Epicardial hemorrhage.
  - Moderate pulmonary congestion.
  - Swollen red liver.
  - Slight hyperemia of upper gastrointestinal mucosa.
- **Birds**
  - Engorged vessels in mesentery and intestinal serosa.
  - Petechiation gizzard.
  - Lungs congested, bloody fluid in air sacs.

  - Swollen hepatocytes with coagulative degeneration.
- **Dogs**
  - Nonspecific lesions:
    - Hepatic, renal, pulmonary congestion, subendocardial, subepicardial hemorrhages.
    - Gastrointestinal hemorrhages.
- **Any species**
  - Acetaldehyde odor in stomach/gastrointestinal tract may help in diagnosis.

Diagnosis

- Acetaldehyde in stomach content, lavage washings, tissues: Submit frozen. Freeze rapidly. Acetaldehyde smells similar to formaldehyde.
- Metaldehyde in baits can be analytically detected.
- Metaldehyde in liver, urine, and plasma. Urinary excretion is low.

Treatment

- Seizure control : Diazepam 2 - 5 mg/kg IV to effect may be preferred over barbiturates because barbiturates compete with an enzyme that degrades acetaldehyde. Phenobarbital or pentobarbital may be required for unresponsive cases.
- Horses : Xylazine with acepromazine has been recommended.
- Artificial respiration.
- Enterogastric lavage, activated charcoal.
- Severe cases : Gas anesthesia, fluids with bicarbonate.
- Fluid therapy to control dehydration, acidosis, electrolyte imbalances.

Key Features

- Especially California and Gulf Coast.
- Snail bait, polymer of acetaldehyde.
- Acidosis.
- Reduction in brain serotonin and norepinephrine.
- Tremors, seizures, not aggravated greatly by stimulation.
- May be followed by liver failure.
- Evacuate GI tract, activated charcoal, diazepam, barbiturates may be contraindicated (use only when not responding), fluids and bicarbonate.

Acetaldehyde toxicity in dogs.

- 600 mg/kg acetaldehyde per os.
- Clinical signs included vomiting, tremors.
- Vomitus often bloody.
- All normal 24 hours after receiving acetaldehyde.

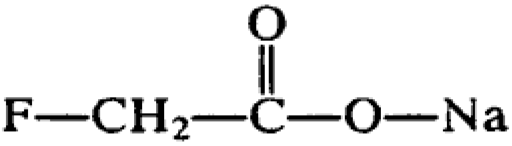
Fluoroacetate-1080

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
All species, esp. carnivores, rodents (target species)	Hours	Few days; often lethal	

Sources

- Primarily used in commercial rodent control (e.g. by Pest Control Operators in very controlled conditions). Not legally found in rodenticides for use in homes in the USA.
  - Tasteless, odorless, colorless; dyed black.

    - Relay toxicosis - especially in dogs, possible in other species.
- Coyote control.
    - Large bait stations - used in past; now illegal.
    - Occasional experimental coyote control permits.
    - Toxic collars (various forms) on sacrificial sheep - on market now.
    - Single lethal dose baits - proposed and studied but not marketed.
- Used for control of ground squirrels and rabbits in some countries.
- Still in use as a widely available rodenticide in some Latin American and other countries of the world. Sometimes products are smuggled into the USA from Mexico.
- Characteristic lag period after ingestion, may limit the development of bait shyness.
- Fluoroacetic acid is the toxic principle in several poisonous plant species from South Africa, Australia, and Brazil (see front index).
- Fluoracetate is an important toxic metabolite of some fluorinated ethanes that might be inhaled, e.g.: 1,2-difluoroethane, 1-chloro-2-fluoroethane, 1-chloro-1,2-difluorethane, and 1-bromo-2-fluoroethane of fluoroethylnitrosoureas. The enzyme involved in bioactivation is likely to be cytochrome P450 2E1.

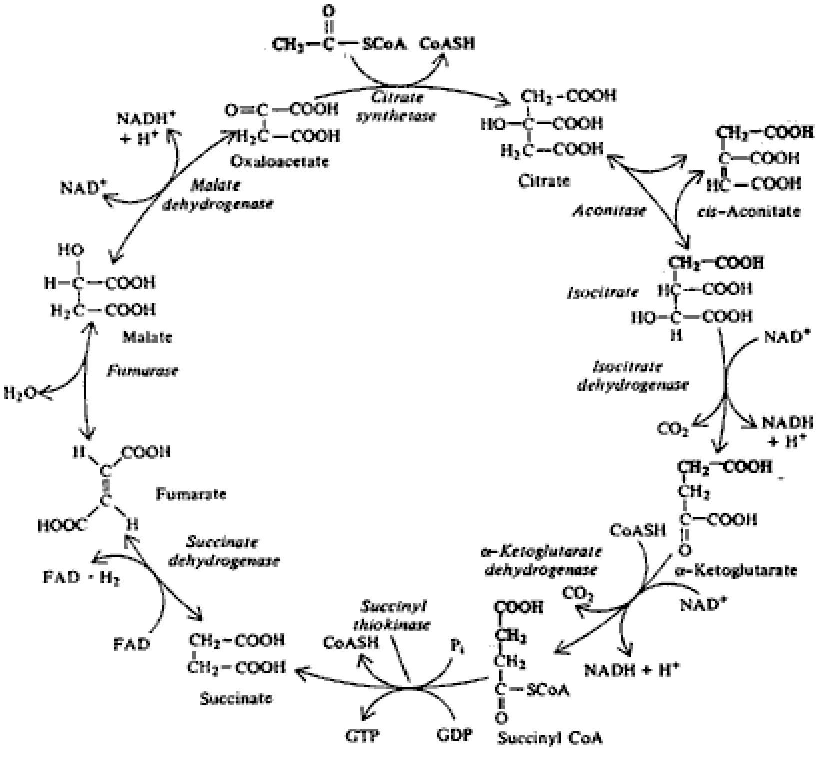


$$F-CH_2-\overset{\overset{O}{\|}}{C}-O-Na$$

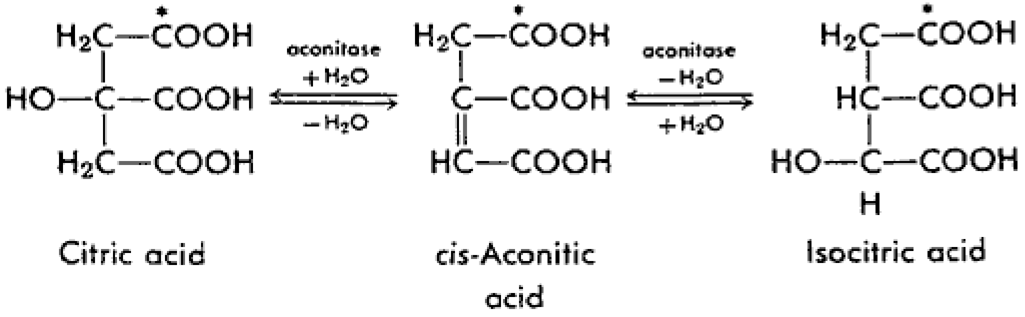
Sodium fluoroacetate (1080)

Mechanism

- **Classical Theory** (Lethal synthesis) :
  Fluoroacetate + Acetyl-Co-A → Fluoroacetyl-Co-A + Oxalacetate → Fluorocitrate
  Inhibits Aconitase (Kreb's cycle inhibited, energy depleted), which results in accumulation of citric and lactic acids.



Tricarboxylic acid cycle



Sites of action of aconitase

- **Kun's hypothesis** (not widely accepted).
    - Fluorocitrate is formed as shown above and is the active (toxic) metabolite.
    - Primary mechanism is not primarily due to inhibition of aconitase - but is due to inhibition of citrate transport across the inner mitochondrial membrane.

Toxicity

- Oral lethal doses (LD_{50}).
    - Canine and feline 0.05 - 1.0 mg/kg of b.w.
    - Rodent 0.2 - 8 mg/kg.
- Oral lethal doses:
    - Cattle: 0.15 - 0.62 mg/kg.
    - Sheep: 0.25 - 0.50 mg/kg.
    - Goat: 0.30 - 0.70 mg/kg.
    - Horse: 0.50 - 1.75 mg/kg.
    - Pig: 0.30 - 0.40 mg/kg.
    - Fowl: 10 - 30 mg/kg.
- Relay toxicoses possible. Occurs especially when canids consume poisoned rodents.

Signs

- Affects CNS and heart.
- Effects and signs vary with species.
- Latent period 1/2 to several hours.
- Cardiotoxic: cattle, horse, rabbit.
- Neurotoxic: dog, guinea pig.
- Both: pig, cat, monkey, sheep.
- **Dogs**
    - Anxiety.
    - Running in a straight line or around the perimeter of an enclosure.
    - Wild barking.
    - Vomiting. Vomiting generally occurs too late to save animal's life.
    - Hyperthermia.
    - Repeated defecation, urination - tenesmus (persistent).
    - Seizures which are largely tetanic; increase in frequency and severity with time. Later, as animal becomes exhausted seizures become weaker but even more frequent. Paddling occurs during seizures.
    - Breathing ceases before heart stops.
    - Death occurs within 2 - 12 hours after ingestion. Death may occur during seizures or from subsequent respiratory paralysis.
- **Cats**
    - Excitation or depression, vocalization.
    - Ropey salivation, possible evacuation of bowels, possibly diarrhea.
    - Arrhythmia common.
    - Generally do not display "running fits".

- **Ruminants, herbivores**
    - Cardiac signs primarily noted : Arrhythmia, rapid weak pulse, ventricular fibrillation. Stagger, tremble, collapse, grind teeth, terminal seizures.
- **Horses**
    - Tremble, sweat. May die from ventricular fibrillation.
- **Swine and sheep**
    - Cardiac and nervous syndromes.

Clinical Pathology

- Hyperglycemia (poor utilization - Kreb's cycle inhibited).
- Lactic acidosis.

Lesions

- Empty stomach, colon, urinary bladder.
- Cyanosis.
- Rapid rigor mortis.
- Congestion - liver, kidney.
- Heart- diastole with subepicardial hemorrhage (nonspecific lesion).
- Sheep that died acutely from fluoroacetate toxicosis had degeneration and necrosis of individual or small groups of myocardial fibers.
- Cerebral edema and lymphocytic infiltration of the Virchow-Robin space have been described.

Diagnosis

- Signs
    - History of exposure, negative tests for other agents help to rule out other causes.
- Analysis of:
    - Baits, stomach contents, vomitus, liver, kidney. Few labs perform analyses; analysis difficult; best lab at present is the State Diagnostic Laboratory in Fargo, North Dakota.
    - False negatives at any lab, especially at inexperienced lab.

Treatment

- Do not use an emetic unless it is very early, no signs are observed, and the animal will be constantly monitored in case of seizures. Perform enterogastric lavage if there is any likelihood of continued absorption.
- activated charcoal + saline cathartic.
- Most symptomatic treatments (when used alone) are not reliably effective after severe signs develop. Treatment often fails but can permit some animals to survive.
- Barbiturates (pentobarbital to control presenting seizures followed by a prophylactic dose of Phenobarbital and additional pentobarbital, repeat as needed) (Tourtellotte and Coon, 1950).
- Solutions containing 50% alcohol and 5% acetic acid have been given orally at 8.8 ml/kg. In almost all cases, this therapy is ineffective. Moreover, combined therapy with ethanol and barbiturates was associated with prolonged (days) anesthesia and a high incidence of pneumonia.
- Barbiturates alone are therefore preferred over barbiturates with ethanol and acetic acid. Barbiturates are far better than ethanol and acetic acid alone.
- Calcium gluconate has been recommended to control tetany (0.2 - 0.5 ml/kg of 5% solution, IV, slowly in fluids).
- Monacetin (glyceryl monoacetate) at 0.55 gm/kg, IM. Apparently, the theory is to provide an available source of acetate to compete with fluoroacetate and thereby increase the production of citrate.
    - Short shelf-life.
    - May be difficult to obtain.
    - Not very effective unless dose of 1080 is near or less than the LD_{50}</.< LI>
- Antiarrhythmics may be of value in appropriate species; apparently these have not been tested for efficacy in 1080 poisoning.

Differential Diagnosis in 1080 Poisoning

- Initial considerations.
    - Lead-running fits, convulsions, vomiting, but usually much slower onset.
    - Hypomagnesemia, hypocalcemia, brain injury.
    - Cardioglycoside toxicosis, Japanese yew (*Taxus* spp.) poisoning.
    - Strychnine, organochlorine insecticide or methylxanthine toxicosis.

Key Features

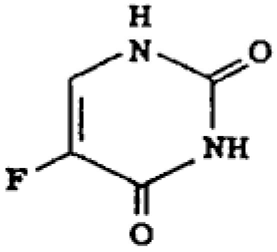
1. Often multiple deaths near source, rodenticide, coyote control.
2. Mechanism(s) of action.
3. Delayed onset, running, evacuation of GI tract, urinary bladder.
4. Species differences (CNS vs. heart).
5. Phenobarbital if seizuring, hyperexcitable, detoxification.
6. Often poor response to therapy.

5-Fluorouracil

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Seizures
All, esp.dogs	Minutes to Hours	Weeks often lethal	

Sources

- Chemotherapeutic anticancer therapy.
- Used for the treatment of solar keratoses, actinic keratoses, and superficial skin tumors in humans.
- Commonly prescribed forms of 5-fluorouracil (5-FU) include 2% and 5% Efudex solution and cream, 1% Fluoroplex topical cream and solution.



5-fluorouracil

Toxicity

- Estimated toxic doses in dog 20 - 129 mg/kg.
- Estimated lethal doses 43 mg/kg.
- Oral LD_{50} 5-FU - mice 500 mg/kg; Rat 100 mg/kg.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Variable oral absorption in human clinical studies.
- Absorbed through intact skin.
- 5-FU is a pyrimidine antimetabolite which needs to be metabolized in order to produce cytotoxicity.
- Its complex metabolism involves intracellular conversion of 5-FU to either 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP) or 5-fluorouridine-5'-triphosphate (FUTP).

- 5-FU readily diffuses across cell membranes, FdUMP does not readily diffuse. Extended bone marrow toxicity may be related to delayed clearance of FdUMP from this site.

Mechanism of Action

- Toxicity of 5-FU is most pronounced in rapidly dividing cell lines.
- FdUMP inhibits intracellular enzyme, thymidylate synthetase. Thymidylate synthetase inhibition prevents the conversion of 2'-deoxyuridine-5'-monophosphate (dUMP) to 2'-deoxyruidine-5'-monophosphate (dTMP). Inhibition of dTMP synthesis results in impaired DNA synthesis.
- FUTP is incorporated into RNA, impairing post-transcriptional processing of ribosomal RNA (rRNA).
- 5-FU can also be converted to 5-fluorocytosine (5-FC) which is incorporated into messenger RNA (mRNA) in place of cytosine, resulting in misreading as uracil.
- Normal RNA turnover may act as a slow release depot for 5-fluororidine-5'-monophosphate (FUMP) which can be converted to FdUMP, with resultant prolongation of FdUMP-mediated blockade of thymidylate synthetase. Incorporation of 5-FU does not necessarily lead to biologically significant alterations in RNA function.
- Postulated from experimental studies in cats that the development of cerebellar ataxia is due to production of fluorocitrate and interference with Kreb's cycle as per toxicosis resulting from fluoroacetate.

Clinical Signs

- Since bone marrow stem cells and epithelial cells of the intestinal crypts have high mitotic index and growth rate, these 2 organs are prime targets for 5-FU toxicity.
- In human patients leukopenia and thrombocytopenia most commonly develop 7 - 20 days following the administration of the first 5-FU dose.
- Mucosal ulceration, diarrhea, and vomiting are common findings during 5-FU therapy in human patients. Radiographic evidence of mucosal ulceration may be noted with the use of contrast media.
- Clinical signs in dogs developed within 45 - 60 minutes following accidental ingestion. Deaths occurred 6 - 16 hours post-ingestion.
- The most commonly reported clinical signs in accidental 5-FU ingestion by dogs include vomiting, seizures, death, hypersalivation, tremors, and ataxia.
- Less common clinical signs in dogs include respiratory distress, cyanosis, depression, lacrimation, alopecia, bradycardia, tachycardia, personality changes - aggressiveness. Behavioral changes have been reported following dermal exposure of a domestic cat to 5-FU.
- Less frequent signs reported in humans include lacrimation, cardiotoxicity, and alopecia which seem to parallel those seen in dogs.
- 5-FU reported to be neurotoxic in man, dogs, and cats. Cerebellar ataxia is most commonly reported neurotoxic sign in human patients receiving 5-FU therapy. Adverse reactions from intravenous 5-FU therapy in dog and cat includes hyperexcitability, nervousness, muscle tremors, and ataxia.

Pathology

- Clinical pathological changes included mild elevations in serum SGPT, serum alkaline phosphatase, and creatinine phosphokinase 2 days postexposure.
- Pathological lesions include hemorrhagic colitis, gastrointestinal mucosal ulceration, desquamation of the gastrointestinal tract, stomatitis. Pulmonary edema and congestion of the lungs, liver, thymus, kidneys, and small intestine.

Treatment

- Emetic and activated charcoal if animal asymptomatic and recent (< 1 hour) ingestion.
- Symptomatic and supportive therapy including fluids, anticonvulsant therapy, and gastrointestinal protectants.
- Valium as an anticonvulsant was rarely effective for the control of 5-FU related seizures. Phenobarbital or pentobarbital may be required as anticonvulsants.
- Phenothiazine tranquilizers are contraindicated. Focal motor and grand mal seizures have been associated with the use of phenothiazine tranquilizers in human patients receiving 5-FU.
- Lithium carbonate (10 mg/kg PO BID) can be used to stimulate myelopoiesis if bone marrow toxicity develops. Accidental ingestions of 5-FU in dogs have not been associated with bone marrow

suppression to our knowledge. Febrile neutropenic animals should have blood cultures performed and require bactericidal antibiotic therapy.

- Continuous subcutaneous infusion of uridine prevented lethal toxicity of 5-FU in experimentally dosed mice. In humans, the proposed dose for uridine rescue is 2 grams/m^2/hour as an intermittent infusion for 3 hours. A 3-hour uridine-free or rest period is recommended between intermittent infusions to avoid risk of uridine-related fever. The usefulness of uridine for the treatment of acute accidental ingestions of 5-FU is uncertain at this time.
- Allopurinol has been studied as an agent to reduce the dose-limiting toxicity of 5-FU. Some benefit in humans was observed with high-dose continuous intravenous infusion. No clinical benefit was noted with bolus allopurinol. Effectiveness of allopurinol in acute oral toxicity is unknown at this time.

Additional Toxicants

<table>
<tr><th>Specific agents</th><th>Major Species</th><th>Usual Time of Onset</th><th>Usual Duration (if survives)</th><td rowspan="4">Full Table for Toxicants Associated with Seizures</td></tr>
<tr><td>Castrix (crimidine) (rodenticide)</td><td>All species</td><td>Minutes</td><td>Hours; potentially lethal</td></tr>
<tr><td>Acute Fluoride Toxicosis</td><td colspan="3">See Toxicants that Affect the Teeth and Skeletal System</td></tr>
<tr><td>Japanese Yew (<i>Taxus</i>) in dogs</td><td colspan="3">See Toxicants that Affect the Heart</td></tr>
</table>

- Castrix (Crimidine)
- Acute Fluoride Toxicosis (See Toxicants that Affect the Teeth and Skeletal System)
- Japanese Yew (*Taxus*) in dogs (See Toxicants that Affect the Heart)
- Corynetoxins (due to ingestion of pasture grasses, such as *Festuca rubra commutata*, that have mature seedheads infected by *Clavibacter toxicus*)

Toxicants Associated with Stimulation or Seizures

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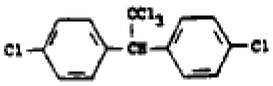
Diphenyl Aliphatic and Miscellaneous Organochlorine Insecticides

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All Species	Minutes to chronic	Hours to days; often lethal	

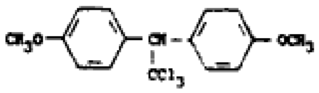
Organochlorine insecticides (OCs) are chlorinated hydrocarbon insecticides. These compounds appear to share the same mechanism with regard to neurotoxicity.

Sources

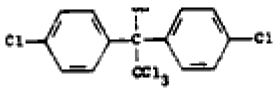
- DDT type (diphenyl aliphatic) - includes DDT, methoxychlor, perthane, and dicofol
    - Methoxychlor used a lot, including products for use around gardens, animals.
- Miscellaneous (mirex, kepone, paradichlorobenzene).
- Paradichlorobenzene.
    - An organochlorine of comparatively low toxicity, but does cause poisoning! Neurologic system toxicity similar to other members of this group. Also, metabolized to a phenolic and is hepatotoxic.
    - In moth crystals, cakes, deodorant block used in diaper pales, closets, restrooms, and in other moth products occasionally including moth balls. (Not same as naphthalene; the most common compound in moth balls).



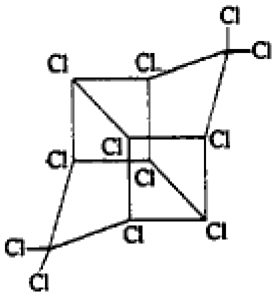
DDT



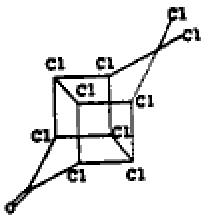
Methoxychlor



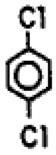
Dicofol



Mirex



Kepone



Paradichlorobenzene

Mechanism of Action of DDT Type Organochlorine Insecticides

- Peripheral nerves and brain:
    - Slows down the turning off of the Na$^+$ influx and inhibits the turning on of the K$^+$ outflux; results in more of each cation inside the nerve than normal. Therefore, the inside of nerve membrane is more positive (partially depolarized)-which decreases the threshold for another action potential to occur. Sensory nerves are more readily affected by DDT than are motor nerves.
    - EEG shows a diffuse low amplitude, fast frequency pattern due to partial depolarization of neurons.
    - Methoxychlor, perthane, dicofol are similar to DDT in structure and mechanism.

  - Methoxychlor has estrogenic effects in rats. Enhances female sexual behavior but reduces fertility (1,3).
  - Methoxychlor is readily metabolized and excreted.
  - Mirex and kepone may have the same neurotoxic mechanism as DDT; however, mirex may also inhibit the postsynaptic binding of GABA.

Toxicity and Signs of DDT Type Toxicoses

- All of these agents mainly cause tremors, salivation, ataxia, depression and sometimes vomiting. Seizures may occur in cats at low doses or in other species with very high doses. LD_{50}s in most species tend to be relatively high. Absorption variable. Typically very fat soluble.
- DDT: unique aspects.
  - Banned in the US in 1972. Still used in some parts of the "developing world".
  - Potent mixed-function oxidase inducer as are its metabolites.
  - Egg shell thinning - birds of prey especially aquatic predators (e.g., bald eagles, ospreys, brown pelicans).
  - O'P'DDD (synonymous with TDE) and especially DDE are persistent metabolites in environment and in body.
  - O'P'DDD - causes thinning of the adrenal cortex in the dog; therefore used to treat Cushing's disease in the dog. Excessive use can cause Addisonian crisis. Potential problem in DDT exposed dogs.
  - See also later - DDT and Metabolites: Reproductive Effects and Effects on the adrenal gland (includes estrogenic activity).
  - LD_{50} rat (oral) for DDT 113 - 2500 mg/kg, rat (iv) 47 mg/kg.
  - Note in humans: toxic signs at 10 mg/kg (oral).
  - Paradichlorobenzene.
    - LD_{50} oral: mouse - 3.2 g/kg, rat - 2.5 g/kg, rabbit - 2.8 g/kg.

Residues

- In addition to acute toxicoses - a primary concern, with regard to the more persistent organchlorines and their metabolites, is residues in the fats of meat and milk. Tendency to store in fat is a function of the rate of metabolism and excretion.
- Since organochlorines were used extensively in agriculture, they are often found in storage or as residues in soil on farms, near feed mills, etc., and can find their way into farm animals, usually via feed.
- Methoxychlor - eliminated fairly rapidly but still had a 30-day withdrawal at one time. More rapid dechlorination and especially oxidation versus DDT.
- DDT - concern regarding cancer, possibly unfounded. Potent mixed function oxidase inducer. DDE, DDT persistent in fat.
- For residue concerns monitor:
  - Milk fat; values may approximate body fat concentrations.
  - Fat biopsy. In cattle, fat may be taken from the tailhead, neck, and scrotum of steers. Prefer to avoid perirenal fat even at necropsy unless other fat is unavailable.
  - Can use experimentally derived data for a particular organochlorine to calculate time needed for a known concentration in body fat to fall below actionable level. **Note**: logical to consult with a veterinary toxicologist when trying to address recommendations for contaminated food animals.
  - Biological magnification--concentration in lipids of successive predators. Can sometimes result in chronic or acute (lethal) toxicoses. Most likely when aquatic systems are involved because: **1**) food chains are longer permitting a greater number of bioconcentrations and **2**) lipid soluble compounds are readily acquired from the environment especially sediments and the surface microlayer of natural waters. These compounds are washed into streams but are poorly soluble in the water column. Sediment concentrations should be checked.
  - Paradichlorobenzene is well absorbed, undergoes glucuronide or sulfate conjugation, and is eliminated over a period of days via the urine and bile.

Diagnosis of Acute Toxicoses

- History of exposure, appropriate clinical signs.
- Brain analysis important for diagnosis of acute toxicosis:
  - Submit half a brain frozen (for organochlorine and other analyses and virology).

    - Other half fixed for histopathology to rule out infectious (encephalitides), degenerative, or neoplastic diseases.
- To determine sources, it may be appropriate to submit specimens for analysis such as:
    - Feed.
    - Suspect insecticidal formulation - granules, liquid, old containers, etc.
    - Gastrointestinal tract contents.
    - Hair (live animal) or skin (dead animal).
    - Liver.
- Fat or milk fat are the preferred samples to assess residue contamination.
- It is essential to avoid any cross contamination: e.g., from source material to animal or milk; or from skin or stomach contents to brain, etc.

Treatment for Acute Toxicosis

- Dermal exposure - bathe with detergent - avoid human exposure by the use of heavy-gauge rubber gloves.
- Recent oral exposure - emetic (small animals and possibly swine) (only if presented very early), and not if any likelihood of seizures is apparent: must avoid aspiration of stomach contents into lungs (as discussed with strychnine previously), lavage. Usually use activated charcoal, saline cathartic.
- Monitor liver function.
- Usually seizure control is necessary for 24 hours or so, sometimes may need to medicate for longer periods of time. Suggested drug for initial control is diazepam (dogs) or, if it fails (or for other species), phenobarbital or pentobarbital. For prolonged CNS stimulation, the drug of choice is phenobarbital which may also stimulate mixed function oxidase activity to shorten half-life.

Decontamination of Residue-Contaminated Livestock

- Identify source and terminate exposure - **essential**.
- Determine value of animals and duration of pasturing/feeding to achieve decontamination. Assess value of animals minus costs of decontamination versus other options. Consider costs including feed, labor, biopsy, analysis, killing and burial of highly contaminated individuals and purchase of additional animals.
- If animals must be destroyed, burial or other disposal should be approved by regulatory officials before euthanasia.
- Lactating animals tend to more rapidly eliminate insecticide residues due in part to losses in milk fat.
- Young animals sometimes metabolize/excrete significant amounts and, because of growth, dilute the residues and may therefore (sometimes) not require specific detoxification procedures.
- Placing fattened animals on pasture, so that they lean out, helps to hasten removal of the organochlorine insecticide from body fat stores. If residues are extremely high in fat, may need to monitor for neurologic effects as body fat residues are mobilized.
- The use of agents to promote metabolism or excretion such as phenobarbital, mineral oil, or repeated activated charcoal for the purposes of lowering residues in fat or milk fat are generally ineffective and not worthwhile.

Gross Lesions

Large doses may sometimes cause centrolobular necrosis of the liver and smaller doses cause liver enlargement (consistent with many inducers of cytochrome P-450).

Key Features

- Mechanism of action-increased Na^+ influx, decreased K^+ efflux, and partial depolarization, tremors, sometimes seizures.
- Cats more sensitive.
- Acute toxicoses, analyze brain, stomach contents, feces, and suspected source.
- Detoxification, pentobarbital or diazepam for seizures.
- Residue problems (not a significant problem with methoxychlor).
- Biological magnification, egg shell thinning especially aquatic raptors with DDT, DDE exposure.
- Residues: terminate exposure, analysis of milk fat or fat biopsy, determine if should detoxify or cull contaminated animals.

Cyclodiene Organochlorine Insecticides and Lindane

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species	Minutes to chronic	Hours to days; often lethal	

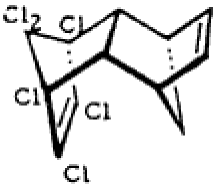
Organochlorine insecticides (OCs) are chlorinated hydrocarbon insecticides.

Sources Cyclodiene type: aldrin, dieldrin, chlordane, endrin, heptachlor, "active constituent" of toxaphene.

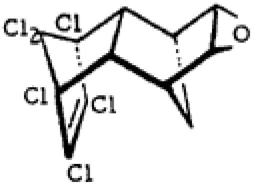
- Chlordane, heptachlor, aldrin used for termites.
- Aldrin used to be used for corn root worm.
- Endrin at least in past used in "Rid-a-bird".
- Relay toxicosis possible (documented with endrin).
- Toxaphene used to be made for animal dips, other uses.
    - Mixed isomers of chlorinated camphene containing 67 - 69% chlorine.
    - High toxicity of the cyclodiene compound 8-octachloroborane makes a very important contribution to insecticidal activity and, therefore, is referred to as the "active constituent" of toxaphene.

Note - Lindane is also called BHC, an abbreviation for the gamma isomer of benzene hexachloride which is a misnomer. Lindane is really hexachlorocyclohexane and must not be confused with HCB. HCB is hexachlorobenzene (true aromatic ring), which was used as a fungicide and is also a significant environmental pollutant because of its extreme persistence and biological magnification, as with many but not all of the organochlorine insecticides.

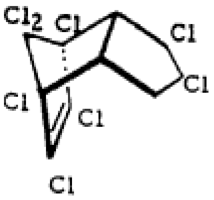
Lindane. Toxicosis is common in cats and dogs. It was never approved for cats, it is used for dogs (fleas, ticks, sarcoptic mange), also for people (Kwell) (for scabies).



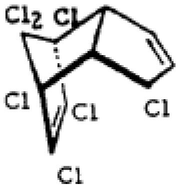
Aldrin



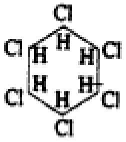
Dieldrin



Chlordane



Heptachlor



Lindane

Toxicity (See Osweiler et al., Clinical and Diagnostic Veterinary Toxicology; 1985.)

- These cause more seizure activity and are more acutely toxic (lower LD_{50}s) than the DDT type organochlorines.
- LD_{50} endrin (cats) 3 - 6 mg/kg.

Mechanism of Neurotoxic Action of Cyclodiene Type OC Toxicoses

- Act by competitive inhibition of the binding of GABA at its receptor - GABA is a more widely used inhibitory transmitter in the CNS than glycine.
- Note the effects of GABA are facilitated by benzodiazepines (such as Valium) and these drugs may therefore be of major benefit in treatment.
- EEG patterns - dieldrin - high amplitude - slow frequency.
- Metabolism in body and environment.
    - Aldrin-dieldrin.
    - Heptachlor - heptachlor epoxide.
    - Dieldrin and heptachlor epoxide are persistent in the body and the environment.
    - It is believed that lindane may also increase threshold by inhibiting GABA-stimulated Cl^- uptake into the neuron (2).

    - Lindane may have an antiestrogenic mechanism.

Signs of Cyclodiene Type OC Toxicoses

- Hypersalivation, vomiting.
- Tremors, ataxia.
- Excitation or less often depression.
- Seizures, pivoting on one foot, fall over backwards.
- Possible liver failure.

Signs of Lindane Toxicoses

- Tremors.
- Excitement or depression.
- Seizures.
- Possible cardiac arrhythmia or cardiac arrest reported in rats.
- Idiosyncratic reaction involving bone marrow depression reported in human beings exposed to lindane. Rare reports of fatal lindane-induced aplastic anemia in humans.
- Some lindane isomers are hepatotoxic and hepatocarcinogenic.

Residues

- In addition to acute toxicoses - a primary concern, with regard to the more persistent organchlorines and their metabolites, is residues in the fats of meat and milk.
- Toxaphene - comprised of chlorinated camphor extract (from pine), therefore many compounds are present. Most are rapidly eliminated. Animal uses recently banned.
- Several cyclodienes appear to be weakly mutagenic but may act as significant tumor promoters especially with regard to estrogen-responsive tumors (See section on other Estrogenic Toxicants). Most of the compounds are persistent in fat.
- For residue concerns monitor:
    - Milk fat; values may approximate body fat concentrations.
    - Fat biopsy. In cattle, fat may be taken from the tailhead, neck, and scrotum of steers. Prefer to avoid perirenal fat even at necropsy when other fat is obtainable.
    - Can use experimentally derived data for a particular organochlorine to calculate time needed for a known concentration in body fat to fall below actionable level. **Note**: logical to consult with a veterinary toxicologist when addressing persistent residue problems in food animals.
    - Biological magnification - concentration in lipids of successive predators. Can result in chronic or acute (lethal) toxicoses (see DDT above).

Diagnosis and Treatment of Acute Toxicoses

- See Diphenyl Aliphatic Organochlorine.
- Recovery may be complete after 3 - 6 hours to a few days of treatment.

Decontamination of Residue Contaminated Livestock

See Diphenyl Aliphatic Organochlorine.

Key Features

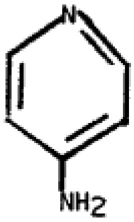
- Mechanism of action: inhibition of GABA causes seizures.
- Acute toxicoses: analyze brain, stomach contents, feces, source.
- Residue problems (fewer problems with toxaphene).
- Biological magnification.
- Diazepam, detoxification, phenobarbital, or pentobarbital for seizures.
- Residues: terminate exposure, analysis of milk fat or fat biopsy, determine if should detoxify or cull contaminated animals.

4-Aminopyridine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, especially target birds	Minutes	Hours; potentially lethal	

Sources

- Avitrol.
    - Bird control agent - usually used in corn - so corn present in GI tract.
    - Baits contain 0.5 - 3.0% of 4-aminopyridine.
    - Also available in concentrated (25 - 50%) form cut with powdered sugar.
- Drug form of 4-aminopyridine is used to antagonize the effects of botulinus toxin or pancuronium bromide. In Europe, used clinically in humans as an antagonist to d-tubocurare. Effective reverser of xylazine sedation and ketamine/xylazine anesthesia in many species <!--[2-4]-->(2,3,4). Recently shown to be effective experimentally to antagonize the effects of two sodium channel blocking toxin, saxitoxin (in red-tide-associated paralytic shellfish poisoning as well as in some neurotoxic blooms of freshwater blue-green algae) and tetrodotoxin (toxin in puffer fish and some toxic newts).



4-aminopyridine

Susceptible Species

- Frequently presented are pigeons, starlings - that fly abnormally, squawk, exhibit involuntary muscle contractions; birds crash, deaths - some with broken necks; skull fractures, etc.
- Sometimes the intent is to poison a few - frighten off rest of birds. In other instances the intent is to kill off entire flock.
- Mammals - of similar sensitivity, poisoning infrequently occurs in dogs, horses and others.

Toxicity

- LD_{50} approximately 20 mg/kg in rats, less in dogs (3.7 mg/kg) and birds.
- LD_{50} dose of 0.5% bait for a 25 kg dog would be 100 mg of 4-aminopyridine or 20 gm of bait.
- Two Quarterhorses that ingested approximately 3 mg/kg exhibited excitability, profuse sweating, convulsions, and death in 2 hours.

Mechanism

- Blocks potassium channels, thereby decreasing the efflux of potassium following an action potential.
- May enhance cholinergic transmission by causing increased release of acetylcholine and other neurotransmitters.
- High doses may elevate cardiac action potential plateau and depress diastolic depolarization.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Can also be absorbed through the skin to reach toxic concentrations.
- Excreted in the urine.
- Rapidly detoxified in the liver.
- No relay toxicosis reported - flesh of the poisoned animal is not considered toxic but GI tract still contains the active ingredient.

Signs
Mammals

- Hyperexcitability.
- Salivation.
- Tremors.
- Incoordination.
- Clonic-tonic seizures.
- Cardiac arrhythmias, tachycardia, increased systolic arterial blood pressure or respiratory arrest.
- Death.
- Liver enzymes may be elevated, metabolic acidosis may occur.
- At doses near the LD_{50}, initial effects are usually noted in 10 - 15 minutes and death occurs 15 minutes to 4 hours later.
- Horses - sweat profusely, convulse, rapid 3rd eyelid flutter.
- Birds.
  - Disorientation.
  - Seizures.
  - Vocalization.
- Man.
  - Metabolic acidosis is a prominent feature.

Diagnosis

- Analysis of stomach contents - consistently get positive results in poisoned animals. Urine and liver may be worth analyzing as well.
- Rapid onset of effects.
- Rapid onset of rigor after death.

Differential Diagnosis

Organochlorine insecticide, acute lead, strychnine, metaldehyde, methylxanthine, tremorgenic mycotoxin, nicotine, and amphetamine poisoning.

Treatment

- Emesis if presented before onset of clinical signs. Gastric or rumen lavage or enterogastric lavage if the emetic is contraindicated or if it fails.
- Activated charcoal and saline cathartic.
- Pancuronium bromide (curare-related drug) antagonizes the effect of 4-aminopyridine and has been (very carefully) used to control seizures in man. Endotracheal intubation should precede administration in case of induction of respiratory paralysis.
- diazepam or phenytoin has also been recommended for seizure control.
- Propranolol (dog, 0.04 - 0.05 mg/kg, IV, slowly) has been recommended for tachyarrhythmias.
- Horses - heavy sedation with xylazine has provided nearly complete relief from excitement and muscle tremors.

Key Features

- Avitrol - corn.
- Birds present in large numbers (especially pigeons) most often poisoned (target species).
- Enhanced cholinergic transmission, muscle contractions, excitation, tremors, seizures, arrhythmias.
- Analyze stomach contents.

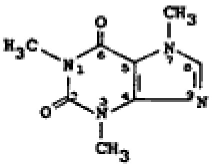
- diazepam, phenytoin or curariform drugs (intubate, artificial respiration as needed), propranolol as needed.

Chocolate, Caffeine, and other Methylxanthines

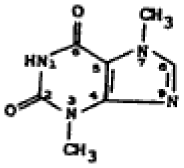
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. smaller dogs	Minutes to hours	Hours; potentially lethal	

Sources

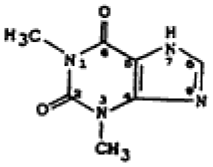
- Most poisonings from methylxanthines occur as a result of chocolate ingestion of dogs.
- Baking chocolate is especially toxic.
- Chocolate toxicoses especially at holidays: Valentine's day, Easter, Halloween, and Christmas.
- Cocoa bean hulls or waste used as bedding for animals has caused toxicosis primarily in horses.
- Second most prevalent poisoning from these agents is a result of caffeine tablets ingested by dogs (often tablets contain 100 mg each).
- Caffeine present in many over the counter medications.
- Caffeine used to hype race horses.
- Theophylline tablets or elixirs used as human or veterinary medication.
    - Readily passed in the milk of exposed lactating animals.



Caffeine



Theobromine



Theophylline

Amounts of Methylxanthines in Chocolate		
	Caffeine	**Theobromine**
Milk chocolate (1 oz)	6 mg	44 - 56 mg
Hot cocoa (6 oz cup)	5 mg	75 mg
Baking chocolate (1 oz unsweetened)	35 - 47 mg	393 mg
Sweet cocoa (1 oz 35% unsweetened	20 mg	130 mg
Dark sweet chocolate (1 oz)	21 mg	134 mg
Semi-sweet chocolate (1 oz)	22 mg	138 mg
White chocolate (1 oz)	0.85 mg	0.2 mg
Oreo cookies (1)	2.4 mg	15 mg

- The theobromine content of cocoa beans is 1 - 2% and that of the hulls are 0.5 - 0.85%
- "Tootsie Rolls" contain 20 mg (caffeine and theobromine) per ounce. Bite sized "Tootsie Rolls" weigh 0.23 ounces

Equivalency of Formulations of Theophylline Derivatives and Salts Compared with Parent Theophylline		
Formulation or Salt	**Trade Name**	**Percent Theophylline**
Theophylline base and theophylline elixir	Various	100%
Theophylline monohydrate	-	90%
Theophylline ethylenediamine (aminophylline)	Various	78 - 86%
Choline theophylline (oxtriphylline)	Choledyl (Parke-Davis)	65%
Theophylline sodium glycinate (Sandoz)	Synophylate (Central Pharm.)	50%
Theophylline calcium salicylate	Quadrinal (Knoll)	48%

Comparative Pharmacokinetics of Theophylline*					
Species	**Peak Concentration after Oral Administration (hours)**	**Elimination Half-Life (hours)**	**Volume of Distribution (L/kg)**	**Percent Bioavailability**	**Recommended Theophylline Dose**
Humans	0.5 - 2.0	9.0	0.5	96%	4 mg/kg every 6 hours
Dogs	1.5	5.7	0.82	91%	9 mg/kg every 6 - 8 hours
Cats	1.5	7.8	0.46	96%	4 mg/kg every 8 - 12 hours

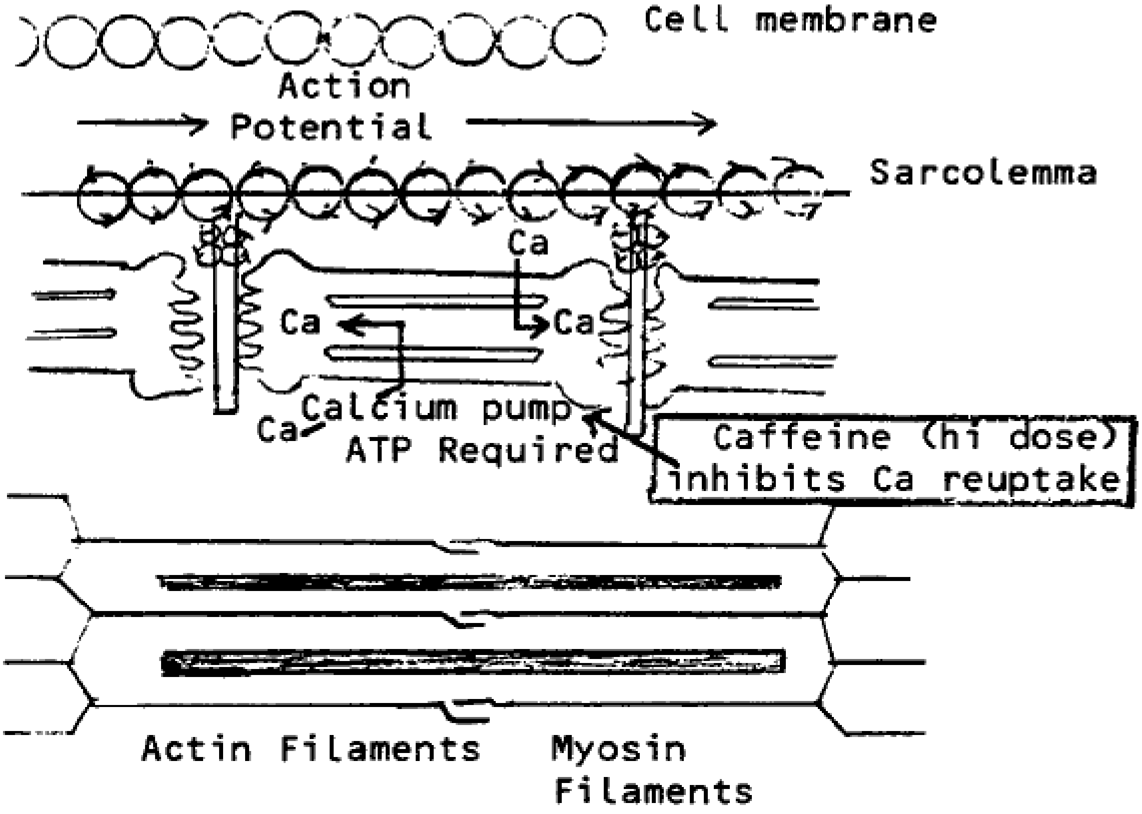
*This table documents regular release formulations of theophylline.

Mechanisms

Gaps in information exist with regard to the relationships between mechanisms of action *in vivo* and those identified in studies performed *in vitro*.

Effects

- *Greatest sensitivity* (definite clinical relevance): competitive antagonism of cellular adenosine receptors. Inhibition of adenosine receptors is likely to account for the behavioral effects and some of the other physiologic effects at therapeutic levels of exposure of methylxanthines. Inhibition at adenosine receptors is also presumably involved in effects noted at toxic doses. Adenosine receptors are linked through guanine nucleotide-binding regulatory proteins (G proteins) to adenyl cyclase and to other effector systems. One adenosine mediated effector which is thought to function independent of adenyl cyclase is a type of K^+ channel in cardiac (atrial) tissue. Inhibition of adenosine receptors causes CNS stimulation, constriction of some blood vessels, and tachycardia.
- *Intermediate sensitivity* (definite clinical relevance): inhibition of calcium sequestration due to methylxanthine induced inhibition of Ca^{++} reuptake. The net effect is increased free Ca^{++} and associated increases in contractility of skeletal and cardiac muscle.
- *Least sensitivity* (uncertain clinical relevance): inhibition of phosphodiesterase. Although historically regarded as of intermediate sensitivity (less sensitive than inhibition at adenosine receptors and more sensitive than reduced reuptake of Ca^{++}), it is now less clear. It appears that concentrations capable of inhibiting phosphodiesterase sufficient to increase cyclic AMP concentrations are unlikely to be seen *in vivo* except, perhaps, after massive overdoses of methylxanthines. Increases in cyclic GMP are somewhat more likely to occur *in vivo* than are increases in cyclic AMP.
- *Other effect* - (clinical importance unclear): Competition for benzodiazepine receptors in the brain.



Excitation-contraction coupling in the muscle, showing an action potential that causes release of calcium ions from the sarcoplasmic reticulum and then reuptake of the calcium ions by a calcium pump.

Toxicity

- Similar in different species: dogs affected most due to eating habits. Theophylline LD_{50} in dogs 300 mg/kg, cats 700 mg/kg. Caffeine and theobromine LD_{50}'s in the dog are 140 mg/kg and 250 - 500 mg/kg, respectively.
- Animals that are more sensitive than average may die at less than LD_{50} doses. Therefore, less than 2 ounces milk chocolate/kg bw or 10% this amount of baking chocolate could comprise a lethal dose.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorption rapid after oral or parenteral administration.
- Parenteral administration does not prevent the development of some clinical signs of toxicoses, e.g., vomiting. GI signs are, at least in part, a result of plasma concentrations of methylxanthines.
- Enterohepatic recirculation after excretion in bile.
- Liver microsomal enzymes promote the metabolism of caffeine. The compounds also undergo N-demethylation and phase II conjugation reactions.
- Also eliminated in the urine.
- Very little parent methylxanthine compound is passed in the feces.
- Half-life of theobromine in dogs is comparatively long (17.5 hours) which also predisposes the species to chocolate toxicoses.
- Half-life of caffeine in dogs is 4.5 hours.

Signs

- Vomiting (common initial sign), diarrhea, diuresis, restlessness, hyperactivity, tachycardia, PVCs, tachypnea, ataxia, tremors, seizures, weakness, coma, cyanosis, hypertension. May "bounce" when picked up and dropped a few inches onto feet.
- Possible hyperthermia, dehydration.
- Diuresis and vomiting may coincide with hypokalemia.
- Death from cardiac arrhythmias or respiratory failure.
- Horses exhibit anorexia, diarrhea, violent excitement and death.

- Teratogenesis: all 3 methylxanthines are teratogenic in laboratory animals.

Diagnosis

- Exposure, clinical signs.
- Submit frozen plasma, urine, stomach contents (frozen).

Lesions

- No specific lesions.

Treatment

- Avoid erythromycin, corticosteroids (they interfere with excretion of methylxanthines).
- Monitor EKG: Do not use lidocaine in the cat! **Note**: in other species for ventricular-origin tachyarrythmias use lidocaine (1 - 2 mg/kg IV until effect, 40 - 60 mg/kg/minute infusion rate to effect to maintain); if it fails, metoprolol (Lopressor®; Betaloc®) injection is preferred over propranolol - since metoprolol does not slow renal excretion of methylxanthines as propranolol can.
    - Metoprolol may be difficult to purchase. Suggested starting dose for injectable form of either metoprolol or propranolol is 0.04 - 0.06 mg/kg, which can be repeated tid and increased if needed. The rate of administration should not exceed 1 mg/2 minutes IV.
    - β blockers can cause decrease in cardiac output and hypotension; monitor EKG.
- For bradycardia (less prevalent) use atropine at 0.04 - 0.08 mg/kg IM or SC (avoid doses causing gut stasis in cattle and horses).
- Artificial respiration if needed.
- If presented before signs, emetic; later use activated charcoal and a saline cathartic whether or not emetic was given. Repeated oral doses of activated charcoal are of additional benefit in shortening half-life (of serum theophylline).
- After signs-if vomiting is controlled, activated charcoal is given and repeated every 3 hours for up to 72 hours; saline cathartic (first 2 treatments only) or, for massive overdose, enterogastric lavage then leave activated charcoal in tract.
- diazepam for seizures; if that fails use phenobarbital and, if needed, pentobarbital.
- Catheterize urinary bladder to prevent reabsorption from urine in the bladder; fluids may also enhance excretion somewhat and counteract circulatory impairment.
- Cannot ion trap and peritoneal dialysis is ineffective.
- Crosses placenta and also excreted in milk: young may be affected (stimulated); also teratogenic in lab animals, therefore, of concern in humans as well.

Key Features

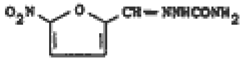
- Chocolate in dogs, caffeine tabs, cocoa bean hulls and wastes in large animals.
- Central, peripheral and muscular mechanisms of action.
- GI effects, PVCs, tachycardia, stimulation, tremors, seizures, coma, arrhythmias, respiratory failure, cyanosis.
- Avoid erythromycin, corticosteroids.
- Evacuate GI tract, activated charcoal with osmotic or saline cathartic twice at 3-hour intervals. Repeat activated charcoal every 3 hours for up to 72 hours.
- Catheterize bladder.
- diazepam or phenobarbital or pentobarbital, lidocaine, metoprolol or propranolol for tachyarrhythmias; atropine for bradyarrhythmias.

Nitrofuran Toxicosis

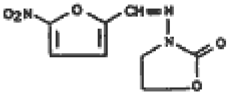
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. cattle, poultry	Hours to weeks	Days; often lethal	

Sources

- Incriminated nitrofurans include: nitrofurazone, nitrofurantoin, and furazolidone. Toxicoses associated with overexposure.
- Toxicosis is apparently infrequently recognized.
- Used as a feed additive for swine and poultry. Not labeled for use in cattle.



Nitrofurazone



Furazolidone

Mechanism

- May be related to inhibition of energy metabolism. Increases occur in pyruvate and lactate. May also inhibit enzymes responsible for the oxidation of succinate, lactate, and glycerol.
- Furazolidone antagonizes the utilization of thiamine in poultry.

Signs

Ducks	Growth retardation, ascites, cardiomyopathy.
Chicks	Depression or hyperexcitability with convulsions, rapid onset. Deaths may follow.
Chickens	Delayed onset of egg production and reduced hatchability. Abnormal posture and loss of balance. Weight loss.
Turkeys	Cardiomyopathy, increased death losses.
Bovine	Depression of weight gain. Arched backs, tremors, circling and convulsions. Hyperirritability, running "fits". May see weakness, ataxia, and paralysis. Onset may be after several days on the medication.
Horses	Inappetance
Swine	Ataxia, especially in the rear; trailing of the rear limbs. Alternatively, hypermetria of the rear legs may occur. Signs aggravated by excitement. Lateral recumbency and paddling. Recovery after 3 days on clean feed.
Goats	Hyperexcitability, tail wagging, chewing, circling, salivation, diarrhea, colic, anorexia.

Diagnosis

Difficult. Feed analysis may be possible but are often difficult to obtain, standards will likely have to be obtained by the laboratory (from the manufacturer).

Pathology

- Goats treated with furazolidone.
- Slight congestion in brain, liver, kidneys.

- Histopathological findings included fatty changes in kidney tubules, fatty changes, and centrilobular necrosis of hepatocytes and dilation of sinusoids (venous congestion).
- Congestion in white matter of cerebellum and scattered vacuoles around nerve sheaths.
- Clinical pathological changes included increase in serum amonia, urea, creatinine, potassium, and SDH activity; hypocalcemia.

Treatment

- Terminate exposure and supportive or symptomatic therapy.
- Thiamine may have some benefit (goats).

Dicentra cucullaria - Dutchman's Breeches and other *Dicentra* spp.

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores	Minutes to hours	Minutes to hours; poisoning is rare	

Description

- Small, somewhat parsley-like plant, soft growth. Flowers, source of the common name, white or pink with yellow tips.
- Related plant, squirrel corn, has underground corn-like tubers, not toxic, according to some sources; other sources say this and other related species should be regarded as toxic.
- Do not confuse with *Thamnosa texana*, a plant of the southwest USA, also known as Dutchman's breeches.

Habitat

- Eastern half of the USA, grows in the midwest.
- Fatal poisoning reported in mountains of Virginia.
- Wooded areas, moist open areas in open woods.
- Other species southern USA and westward to California.
- Green and may be plentiful before other forage is abundant in the spring.

Toxic Principle

Isoquinoline alkaloids.

Toxicity

Danger of poisoning appears to be much less by the middle of May; high altitude hazard may persist as late as June.

Susceptible Species

- Cattle may be much more sensitive than sheep.
- Infrequent cause of poisoning overall.

Signs

- Trembling, running back and forth with the head held high.
- Salivation.
- Vomiting, including vomiting of rumen contents.
- Abdominal pain.
- Possible dyspnea.
- Trembling becomes continuous.
- Prostration.
- Convulsions and opisthotonus.
- Acute course.

- Rarely fatal.
- Recovery from poisoning is rapid.

Lesions

Nonspecific.

Treatment

- May recover in a few hours without treatment.
- Appropriate to administer activated charcoal and, if hydration is adequate or after it is restored, to use a saline cathartic as well.
- activated charcoal may be mixed in feed if just exposed and asymptomatic or minimally affected (early in course).
- Symptomatic and supportive care.
- Supplemental feeding may reduce consumption to subtoxic amounts.

Prevention

Prevent access to the plant.

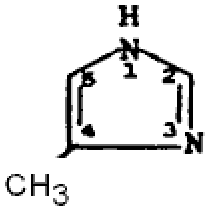
4-Methyl-Imidazole

(Bovine Bonker's Syndrome; Ammoniated Feed Syndrome)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. ruminants	Minutes to days	Hours to days; often lethal	

Sources

- 4-Methyl-imidazole (4-MI) is formed as a result of ammoniation of feeds in an attempt to increase the feed value of low and medium quality forages. A Maillard reaction occurs = a condensation of an amino group with a reducing sugar.
    - Ammoniated molasses.
    - Ammoniated higher quality forages such as forage sorghum, hybrid sudan, cereal grain, brome, fescue, alfalfa, wheat, and bermuda hays.
    - Ammoniated wheat straws, corn stalks, and corn silage are less often a problem, since they contain low levels of soluble sugars which are necessary for the formation of 4-MI.
    - Ammoniated straw is reportedly made more toxic as a result of heat build-up from wrapping treated bales in black plastic.
- Metabolites (not 4-methyl-imidazole itself but still toxic) in the milk of cows fed ammoniated forage or molasses.



4-methyl-imidazole

Toxicosis

Fairly uncommon, not rare.

Toxicity

- Pyrazines and imidazoles are formed as a result of the ammoniation of feeds.
- 4-MI is formed as a result of a nonenzymatic reaction (Maillard reaction) caused by the condensation of an amino group and a reducing compound (amino acid and reducing sugars).
- Pyrazines are considered to be nontoxic.
- 2-MI and 4-MI are known convulsant agents in mice; 4-MI is more potent than is 2-MI.
- Adult cattle, calves and other nursing animals [by virtue of the passage of active metabolites (not parent compound) in the milk] may all be poisoned.
- Occasionally, only calves affected. When calves were affected (and the cows nursing the calves acted normally), 40 - 120 ppm of 4-MI was found in incriminated forages. The threshold concentration for toxicosis, however, has not been established.

Signs

- Onset: rapid or up to weeks after start on treated hay.
- Mouth chomping, salivation, impaired vision.
- Hyperexcitability, wild running, circling, seizures, death.
- Lactating cows may be more resistant than forage-eating calves (onset may occur after several days of feeding depending on concentration).
- Nursing calves may be affected even more rapidly (onset may occur within 2 days of the first feeding of the cows).

Diagnosis

- Clinical signs, history of intake of appropriate ammoniated foodstuff; identification of 4-MI in significant amounts in ammoniated forage, molasses or complete ration.
- No lesions on postmortem.

Treatment

- No treatment known.
- Terminate exposure, symptomatic control of hyperexcitability if severe, seizure control (barbiturates or chloral hydrate).
- Symptomatic and supportive care.
- Try activated charcoal and a saline cathartic (no studies yet).

Water Deprivation - Sodium Ion Toxicosis

(Could be called "water-deprivation-sodium toxicosis-water toxicosis")

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. swine, cattle, poultry	Minutes to days	Hours to days; often lethal Permanent brain damage possible	

Susceptible Species

- The problem of salt poisoning and water deprivation in swine occurs also in virtually all other species. Swine are the most sensitive of the domestic animals. Horses are next, while sheep are more resistant and cattle are intermediate in susceptibility. Lactating cows are less tolerant of excessive salts in the water or diet than are other cattle. Poultry are also commonly affected.

- Major problem in swine and poultry; most problems in ruminants occur in cattle in the western states.
- Dogs occasionally affected; serious toxicosis is rare.

Sources and Conditions that Commonly Lead to Illness

Swine

- Salt is an essential nutrient. It is also added to the ration to either increase or decrease palatability. Normally 0.5 - 1% of ration.
- Primary problem is usually water deprivation.
    - Mechanical failure of waterers.
    - Neglect, overcrowding.
    - Medicated water unpalatable.
    - Animals fail to find water (new surroundings).
    - Frozen water.
- High salt intake increases water requirement which increases risk. Sources may include:
    - Sodium sulfonamides.
    - Poultry wet mash made with whey or brine.
    - High salt alone usually no problem unless fresh water restricted.
    - Toxic dose of sodium chloride quoted for cattle is 2.2 gms per kg of body weight. Diets containing 2% sodium chloride do not create problems unless water is restricted.
    - Sodium in water is more hazardous than in feed (water intake exceeds feed intake and no compensatory advantage to drinking more).
    - Salt used to control intake of protein block, mineral supplement, etc., esp. if animals unaccustomed.
    - Dogs sometimes eat rock salt, usually causes vomiting and not much else. Occasional concern: excessive use of salt as an emetic.
    - Gastroenteritis, diuresis; combine to cause dehydration which increases hazard of excess sodium.
- Aggravated by unlimited access to fresh water following water deprivation or following episode of high sodium intake (water toxicosis).

Cattle

- Acute form occurs when excessive amounts of salt are ingested causing an irritant gastroenteritis. Dehydration results and is aggravated by the increased osmotic pressure within the alimentary tract. Some salt is absorbed. Hemoconcentration and salt absorption cause increases in serum and CSF sodium concentrations. Can cause some CNS signs in addition to GI signs.
    - More likely in semiarid areas for several reasons: water supplies in lesser supply and easily dried up; lower humidity and higher temperatures tend to greatly increase water losses from the animals. Water supplied from natural springs and deep wells and water contaminated with run-off from oil well drilling may contain high levels of sodium chloride, calcium sulfate, and calcium carbonate. Any of these salts in water and especially calcium carbonate markedly reduce water consumption when cattle are first exposed to them.
    - Other causes: a sudden change from fresh water to salt water when animals are thirsty, and water accumulation in salt troughs during drought periods.
    - Improperly mixed rations or attempts to limit protein supplement intake by "spiking" it with salt. Also, inadequate trough space increases the likelihood of gorging on concentrate, which may result in excessive sodium intake even with lower amounts of salt in the concentrate.
    - Feeding urea can increase the likelihood of Na^+ toxicosis by elevating: **1**) urinary output, **2**) anhydremia, and **3**) sodium concentrations in the brain.
    - Lethal toxicosis in ruminants (especially cattle) is often associated with saline waters (especially on range) or other excessive exposure to a source of salt. Brine from oil well drilling.
    - Sulfates can cause diarrhea and dehydration. Note sulfates used as saline cathartics.
    - Saline waters that may be safe for cattle in the winter can be deadly in summer months.
    - Total salt content of water is more important than any one salt. Total salts in water should not exceed 1.0% for cattle. Older references have suggested up to 1.5% total salts for nonlactating cattle.
    - Fluorine and magnesium salts have a much greater adverse effect on the alimentary mucosa than does sodium.

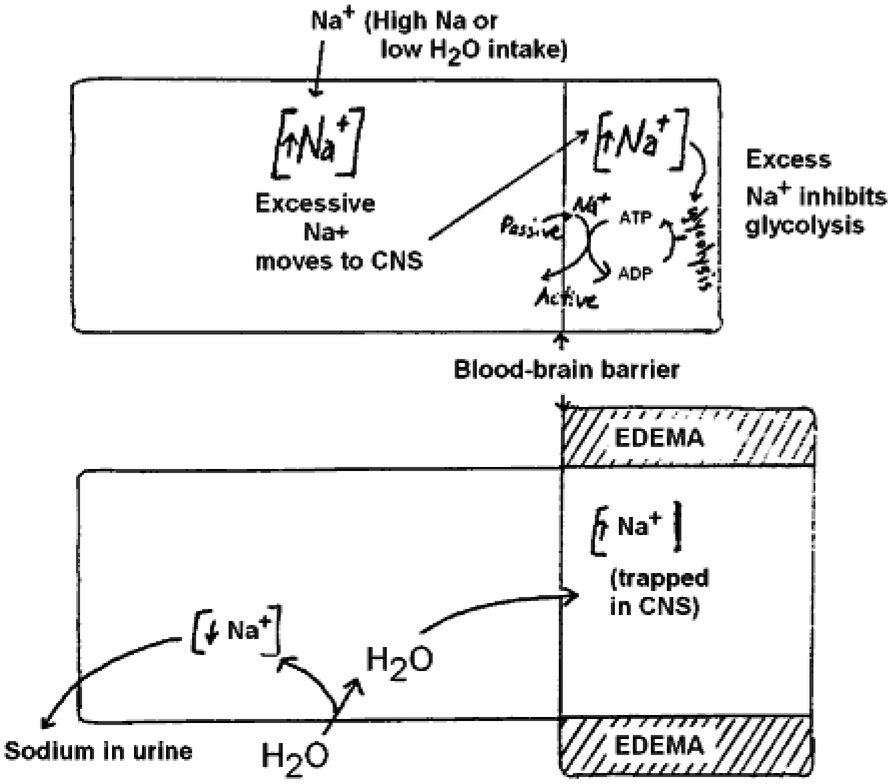
- Water deprivation in the presence of normal sodium intake results in serious metabolic disturbances when cattle have lost 10% of their body water. Losses of 20 to 25% of body water are almost always fatal. Metabolic changes taking place in cattle deprived of water include:
    - Loss of weight due to reduction in tissue water and due to actual breakdown of body substance in an effort to furnish water for physiologic needs. First, fat and carbohydrate are used for this purpose and later protein.
    - Acid-base disturbances occur usually toward the acid side.
    - Obviously hemoconcentration occurs with associated polycythemia, increased plasma protein, and increased chloride and sodium.
    - Body temperature, pulse rate, and cardiac output all increase.
    - Nonprotein nitrogen increases presumably as a result of increased osmolarity of the blood resulting in decreased glomerular filtrate production and perhaps due to the increased protein catabolism mentioned above.
    - Drying out of mucous membranes, subcutaneous tissues and skin takes place.
    - Terminally, uremia, exhaustion, and collapse takes place.
- High salt consumption or water deprivation followed by unlimited access to water typically results in cerebral edema and neurological signs (water toxicosis).

Toxicity

- Acute oral lethal doses.
    - Horse, cattle, swine: 2.2 g/kg.
    - Dog: 4 g/kg.
    - Sheep: 6 g/kg.
- Affected by salt concentration and availability of water.

Mechanism (theory)

- Sodium is rapidly absorbed from gut, distributed throughout body.
- Normal animal.
    - Plasma Na^+ 135 - 155 meq/1 (mean 143.3 ± 6.5).
    - CSF Na^+ 135 - 150 meq/1 (mean 139.6 ± 5.2).
- Na^+ passively diffuses into CSF, but requires active transport to be removed from the CSF (energy required).
- With dehydration, high Na^+ in plasma diffuses into CSF; high Na^+ depresses glycolysis, therefore energy for active transport deprived. Na^+ accumulates in CSF.
- Rehydration with access to fresh water results in dilution and excretion (in urine) of excess sodium; plasma sodium returns to normal.
- Sodium trapped in CNS, attracts water due to osmotic gradient.
- Cerebral edema and resultant clinical signs.



Proposed mechanism of action

Signs

- **Swine**. Nervous signs often include disorientation probably due to cerebral edema. (Signs described below are typical of a primary problem of water deprivation in swine.)
    - Thirst, colic, vomiting, diarrhea, pruritis, constipation (usually missed). Polyuria, late anuria.
    - Onset of nervous signs after 1 - 5 days of water restriction/deprivation.
    - Aimless wandering and circling, snout may twitch.
    - Head pushing, pivoting around one foot is common.
    - May not eat or drink.
    - Blindness, deafness, or at least nonresponsiveness in some animals.
    - Pigs dog-sit, tremor, jerk head back, fall over into clonic-tonic seizures with opisthotonos, paddling, death.
    - Morbidity varies due to salt intake, water availability, environmental conditions.
    - Mortality: averages 3 - 20%; about half of those with clinical signs die.
    - Rapid rehydration will cause more acute neurologic signs.
- **Poultry**. (Signs described are typical of a primary problem of water deprivation in poultry.)
    - Thirst, dyspnea, fluid discharge from beak, wet droppings.
    - Weakness or paralysis of hind limbs. No motor excitation.
- **Cattle**. The initial effects vary. Principle signs include weakness and dehydration. Severe water deprivation followed by access to water result in the following clinical signs in cattle:
    - Belligerent behavior.
    - Aggressiveness in getting to water supplies. This is mentioned because it makes it difficult to administer water gradually and is hard on water tanks.
    - Sucking in air as well as water with secondary bloat.
    - Incoordination.
    - Bellowing as if in severe pain.
    - Fasciculation of fascial muscles.
    - Ear twitching.
    - Sticking the tongue out with the head outstretched as if painful in the pharyngeal area.
    - Fence walking and aimless wandering.

  - Some animals may have blindness, convulsive seizures followed by partial paralysis and knuckling of the fetlocks.
  - Diarrhea, constipation.
  - May appear normal but sometimes when approached take 3 - 4 steps and collapse pushing the muzzle into the ground.
  - Animals have been known to drown in creeks unable to rise.
  - Dairy cows may develop acetonemia.
  - Some animals abort.
  - Nursing calves are far less affected than adults by water deprivation. Waters high in salt can cause the opposite effect, that is cessation of milk production before damage to the cow is apparent.
  - Sometimes hooves are sloughed.
  - Those animals that develop knuckling of the fetlock joints may secondarily develop damage to the tendons, peripheral nerves, and associated tissues in spite of showing no evidence of pain.
  - Some animals develop hemolysis, hemoglobinuria, and potentially anemia.
  - Blindness, tonic-clonic convulsions, and terminal coma occur.
- When excessive salt intake is a primary factor in cattle, one can expect more gastroenteric signs due in part to the irritating effects of the salts. These include:
  - Anorexia.
  - Mucus in the feces.
  - Diarrhea.
  - Vomiting.
  - Death within 24 hours.
  - Additional signs may include constant polyuria and a nasal discharge.
- **Dogs**. Signs typical of ingestion of rock salt include:
  - Vomiting, gastrointestinal upset.

Pathology

- **Swine**.
  - First 48 hours-eosinopenia, eosinophilic cuffs around vessels in cerebral cortex and adjacent meninges (eosinophilic meningoencephalitis).
  - Cerebral edema, early necrosis, malacia.
  - After 3 - 4 days-eosinophilic cuffs no longer present; see enlarged perivascular spaces left behind in some cases; eosinophils reappear in blood.
- **Cattle**.
  - No eosinophilic cuffs.
- Gross lesions in cattle with sodium ion poisoning, water deprivation, water intoxication may include:
  - Congested mucosae of the small intestine, omasum, and gall bladder.
  - Edematous lungs with moderate congestion.
  - Fluid feces.
  - Edema on ruminal surfaces associated with hemorrhage in the area adjacent to the gall bladder.
  - Edema around the major bile ducts.
  - Enlarged liver.
  - The brain appears firm, white, and swollen.
  - Polioencephalomalacia.
  - Decreased clotting of the blood postmortem (possible DIC).
  - May see leg lesions.
  - Often no gross postmortem findings.
  - Histopathologic findings include:
    - Dilation of mucosal and submucosal lymphatics in the duodenum.
    - Small foci of necrosis in the liver and renal medulla.
    - Leakage of eosinophilic material from glomeruli into Bowman's capsule.
- **Poultry**.
  - Edema of tissues.
  - Urate nephritis if saline water.

Diagnosis

- History (if poor husbandry involved may be hard to get person to admit what happened).

- Serum and CSF Na^+ concentrations of over 160 meq/1. In water deprivation/ Na^+ ion toxicosis, CSF Na^+ usually exceeds serum Na^+, unlike the situation in the normal animal.
    - Urine chloride increases and specific gravity decreases.
    - The PCV does not decrease much since water is apparently evenly distributed, at least in some cases, between plasma and RBCs.
- Brain (cerebrum) Na^+ usually exceeds 1800 ppm; often 2000 - 3000 ppm.
    - **Note**: If thorough rehydration has occurred and time has elapsed, the brain Na^+ may be normal. Also water deprivation and excessive serum and brain Na^+ concentrations may result from any other condition which prevents animals from drinking-includes other toxicoses, trauma, encephalitis, etc.
    - Ship half of brain to laboratory frozen (for analysis and virology).
    - Ship other half to the laboratory fixed in formalin.
    - Collect a complete set of tissues for toxicology and pathology in case the presumptive diagnosis is incorrect.

Differential Diagnoses

Toxicosis due to lead, organochlorine, organophosphorus or carbamate insecticides, carbon monoxide, cyanide, metaldehyde, nicotine, and certain poisonous plants; as well as encephalitis, trauma, polioencephalomalacia, heat stroke, gut edema.

Treatment

- Small amounts of water frequently (limit access), try to correct energy balance; i.e., hand feeding, symptomatic supportive care.
- Remove source of excess sodium if one is present.
- No largely successful therapy known. Natriuretic diuretics and anticonvulsants generally do not help.
- In extremely valuable animals or small animals the temporary use of hyperosmotic fluids (not hyperosmotic with excess sodium; instead use dextrose or other substance) may be worthwhile.
- In humans, treatment of sodium ion toxicosis/water deprivation/water intoxication with 50 - 100 ml of 5% saline has been used hourly until seizures are controlled. Monitoring to ensure that plasma sodium does not go too high is necessary. In two other human cases, therapy consisting of hypertonic glucose solutions containing physiologic quantities of balanced electrolytes IV has been effective ireating dehydration and subsequent water intoxication. This course of action would appear to be more logical than treatment with saline solution.
- IV administration of dextrose and electrolytes was effective in saving some cattle after failure with water alone. Thus, hypertonic solutions (low in sodium) are recommended.

Key Features

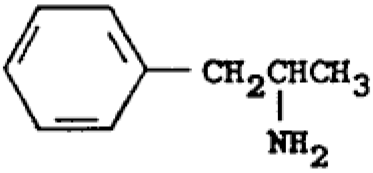
- Excess salt intake and deficient fresh water or just the latter.
- Acute exposure: GI signs.
- Swine - eosinophilic cuffs in brain, eosinophilia: both transient.
    - CNS signs, disoriented.
- Cattle - no eosinophilic cuffs, may be belligerent, aggressive around water source, may drown after get to water; may damage soft tissues of legs.
- Diagnosis - brain, CSF, and serum sodium; histopathology; rule out other causes.
- Treatment - limited water intake, IV hypertonic solution (not NaC1). Supportive, symptomatic.

Amphetamine Toxicosis

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Small animals, horses	Minutes	Hours to a day or so; potentially lethal	

Sources

- Poisoning may be a result of exposure to illicit drugs and the caller may be reluctant to divulge the drug involved.
- Animal chewing up an owner's prescription bottle or eating spilled medication.
- Tablets often 5 - 10 mg each.



Amphetamine

Toxicosis

- Uncommon, not rare.
- Estimated LD_{50} 10 - 30 mg/kg.
- Deaths (man) reported following ingestions as low as 1.3 mg/kg of metamphetamine.

Mechanism of Action

- Most important mechanism: stimulates catecholamine release centrally and from adrenals; stimulate cortical centers including cerebral cortex, medullary respiratory center, reticular activating system.
- Sympathomimetic compound-stimulates at sympathetic nerve endings greater stimulant activity than norepinephrine.
- Inhibits monoamine oxidase.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rapid absorption from GI tract.
- Enters CSF, CSF concentrations reported to be 80% of plasma concentrations.
- Elimination dependent on pH. Acidic pH shortens elimination half-life.

Differential Diagnosis

Strychnine, organochlorine insecticide, methyxanthine, 4-aminopyridine, metaldehyde, other illicit drug toxicoses.

Signs

- Similar cardiac and CNS effects to those seen in methylxanthine toxicosis.
- Seizures are infrequent, but can occur.
- Coma may sometimes be seen.
- Hypertension, hyperthermia, lactic acidosis, hypoglycemia.
- Mydriasis, tachycardia, hypertension, arrhythmias, occur in man; less commonly vomiting, diarrhea, dysuria, urinary retention.
- Renal failure secondary to rhabdomyolysis, dehydration sometimes reported.
- Hyperthermia, hyperventilation.

Diagnosis

- Presence of tablets in vomitus or gastroenteric contents-confirm analytically if in doubt.
- Plasma concentrations of amphetamine, amphetamine in urine.

Treatment

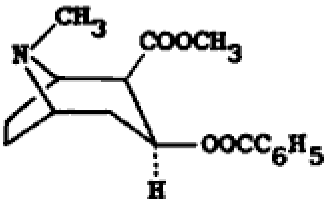
- Early before marked signs: emetic in SA, lavage if ineffective or later when animal is stimulated (after appropriate sedation). Activated charcoal and cathartic.
- Chlorpromazine (10 - 18 mg/kg IV) or haloperidol (1 mg/kg IV) given after administration of a lethal intravenous dose of amphetamine sulfate (10 mg/kg) increased survivability in dogs. Hyperthermia was also antagonized by chlorpromazine and haloperidol.
- Diazepam is effective (oral or IV administration) in man and therefore would probably be effective in dogs. Controls most of the undesirable CNS stimulatory effects.
- Barbiturates are probably adequate in other species, incuding the cat.
- If the body temperature becomes markedly elevated, it is probably wise to employ external cooling (ice, etc.).
- Amphetamine is a basic drug and its excretion can be enhanced by acidifying the urine. **Note**: there are precautions that are essential-acidification is **contraindicated** if the animal is in renal failure for any reason or if severe myoglobinuria from muscle damage is occurring.
- Ammonium chloride or ascorbic acid can be used in small animals to lower the urine pH to the range of 4.5 to 5.5.

Cocaine Toxicosis

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Small animals	Minutes to hours	Hours; potentially lethal	

Sources

- Natural alkaloid from coca (*Erythroxylon coca*).
- Used clinically in a 1 - 4% solution as an eye anesthetic or in 10 - 20% solution as a nasopharyngeal anesthetic. Requires special license.
- Poisoning may result from exposure to illicit drug. Exists as hydrochloride salt or as cocaine base, "crack"
- Note street cocaine is often impure, adulterants include sugar, local anesthetics, phencyclidine, etc.
- Cocaine look alikes commonly include sympathomimetics, e.g., phenyl propanolamine or ephedrine, caffeine, local anesthetics.



Cocaine

Toxicosis

Uncommon.

Toxicity

- Not well established.
- 20 mg capable of killing adult human.

Mechanism of Action

- Local anesthetic effect is related to blocking fast Na^+ channel current.
- Powerful CNS stimulant effect is probably due to inhibition of reuptake of endogenous catecholamines, cocaine is the only local anesthetic with this effect.
- Stimulates dopaminergic neurotransmission by blocking the reuptake of dopamine.
- Pharmacologic effects include vasoconstriction, mydriasis, tachycardia, predisposition to seizures, arrhythmias are believed to be associated with activation of sympathetic system.
- Large doses cause direct cardiotoxicity.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rapidly absorbed from mucous membranes.
- Slightly delayed after oral ingestion.
- Enters milk and readily crosses the placenta.
- Metabolism not understood-plasma pseudocholinesterase and hepatic esterases involved.
- Nearly all is metabolized (only 5% is excreted unchanged in the urine). Other metabolites are eliminated via the urine.

Clinical Signs

- Dogs-experimental IV administration (LD_{100} = 39.5 mg/kg).
  - Hyperthermia. Also suspected as a cause of malignant hyperthermia.
  - Acidosis.
  - Tachycardia.
  - Seizures.
- Accidental poisoning clinical signs dogs and cats.
  - Hyperactivity, erratic behavior, depression, coma, seizures.
  - Vomiting, salivation.
  - Tachycardia.
  - Pulmonary edema, panting.
- The following clinical signs have been reported in human poisonings.
  - Initial tachycardia and hypertension followed by hypotension. Cardiac arrhythmias common.
  - Hyperpnea, respiratory arrest, pulmonary edema.
  - CNS stimulation, seizures.
  - Vomiting.

Treatment

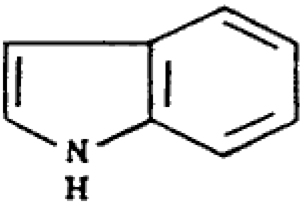
- Early, before clinical signs develop, emetic in small animals, followed by activated charcoal and cathartic. Gastric or enterogastric lavage may be required.
- Seizures if present may be controlled with diazepam.
- Cardiac tachyarrhythmias control-experimental pretreatment with high doses of propranolol (6 - 10 mg/kg IV) prevented development of tachycardia and hypertension. However, coronary vasoconstriction may be increased by propranolol. Because of the relatively short action of cocaine on the heart, usually, the short acting β_1 selective blocker, esmolol, would be recommended with a half-life on the order of 10 minutes, repeated doses of esmolol may be needed. Another β_1 selective blocker to consider using in these cases is atenolol. Its half-life is long, however, at 3 to 9 hours in the dog.
- Chlorpromazine (12 mg/kg IV) pretreatment decreased seizure activity, prevented acidosis, and prevented hyperthermia in dogs that received a lethal IV dose of cocaine. Possible benefit of chlorpromazine is through antidopaminergic effects. May lower seizure threshold. Also consider using if animal is extremely hyperthermic.
- Control hyperthermia by physical means.
- Diuresis, acidification are not effective.
- Fluid therapy if hypotension present.

Tremorgenic Mycotoxins and Various Staggers Syndromes

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
All species, esp. dogs, cattle	Minutes to days	One day to weeks; often lethal in dogs	

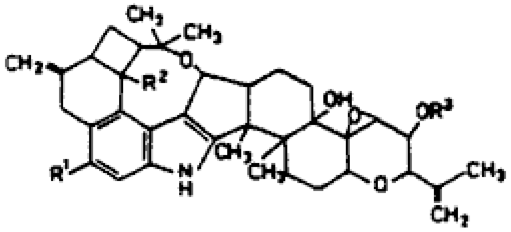
Introduction

Tremorgens are mycotoxins (secondary fungal metabolites) which contain an indole moiety, presumably derived from tryptophan and which produce tremors or seizures in animals consuming toxic amounts of contaminated foodstuffs. There are at least five groups of tremorgens. The penitrem group, the paspalitrem group, the fumitremorgins group, the verruculogen group, and the tryptoquivaline group.

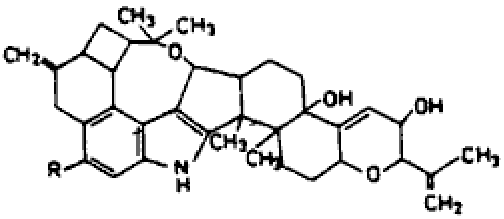


Indole

Structures



Penitrem A, $R^1 = Cl$, $R^2 = OH$, $R_3 = H$
Penitrem B, $R^1 = H$, $R^2 = H$, $R_3 = H$
Penitrem E, $R^1 = H$, $R^2 = OH$, $R^3 = H$
Penitrem F, $R^1 = Cl$, $R^2 = H$, $R^3 = H$
25-O-Acetylpenitrem A, $R^3 = Ac$



Penitrem C, R = Cl
Penitrem D, R = H

1. Penitrem A

Among the more common tremorgens are **Penicillium** mycotoxins, such as penitrem A. In older literature, this compound may appear as tremortin-A.

Sources of Penitrem A Include:

- Moldy refrigerated foods, cottage cheese, cream cheese.
- Moldy walnuts, especially English walnuts in Central to Northern California.
- Moldy peanuts.
- Moldy stored grains, mixed feeds.
- Penitrem A was initially isolated from *P. crustosum*, and so far, intense production has been limited to species of:
    - *P. crustosum*, *P. granulatum*, *P. cyclopium*, *P. palitans*, and *P. puperum*.

Susceptible Species

Include at least the following: bovine, ovine, equine, porcine, canine, rabbit, poultry, and several species of rodents.

Mechanisms

- Increases in resting potential, end plate potential, and duration of depolarization. Influence presynaptic transmitter release.
- Penitrem A facilitates transmission of impulses across the motor end plate.
- Also suggested that penitrem A inhibits glycine where it acts as a neurotransmitter in inhibitory neurons in the spinal cord.
- Verruculogens reduce brain GABA concentrations.

Toxicity of Penitrem A and Penitrem B

- Mice tremor at .25 mg/kg/bw of penitrem A.
- Mice tremor at 1.3 mg/kg/bw of penitrem B.
- LD_{50} penitrem A-1.05 mg/kg.
- LD_{50} penitrem B-5.84 mg/kg.
- Penitrem A is acid labile.

Signs

- Tremors, seizures, and prostration.
- With low doses, fine muscle tremors occur; at high doses, convulsions and possible death may occur.
- Possible sequellae (seen in rats) are Parkinsonism-like signs that last up to 2 weeks.
- Polyuria may occur, possibly attributable to hyperglycemia.
- Dogs tremor from 2 - 4 hours to much longer until death during seizures, or may gradually return to normal over 1 - 2 days.

Lesions

- No specific neurologic or muscle lesions. Trauma from seizures.
- Increased lactic dehydrogenase, creatinine phosphokinase, pyruvic acid, blood glucose.

Diagnosis

- Differential diagnosis: in large animals, the syndrome is most similar to other mycotoxin-associated diseases such as paspalum (or Dallis grass) staggers, and Bermuda grass tremors (both believed to be due to tremorgens).
- For small animals, a bioassay may help in confirmation: 0.5 gram moldy food or stomach contents is emulsified in 2 ml of buffered saline. Mice are given 0.6 ml orally. Signs appear in 10 - 20 minutes and include: hyperirritablity and muscle tremors. Over 2 - 3 hours, mice may have tonic-clonic seizures and opisthotonos alternating with depression and tremors. Some mice die, others recover over 24 hours.
- If standards are available, penitrem A is reportedly rapidly detected on thin-layer chromatography (TLC); when possible, submit suspected source to a laboratory which has standard.
- No specific lesions are seen at necropsy or on histopathology, secondary trauma is possible.

Treatment

- For acute toxicosis, activated charcoal and a saline cathartic are recommended after the animal is appropriately sedated.
- Pentobarbital anesthesia has been advocated for control of seizures.
- Fluids and corticosteroids have been recommended for shock when present; and cold water baths for hyperthermia.
- Drugs that increase glycine in the CNS including mephenesin or nalorphine were shown to be able to abolish penitrem A tremors in mice.

2. Staggers Syndromes

Introduction

- Staggers syndromes have different etiologies but similar clinical presentations. Syndromes include ryegrass staggers, paspalum (Dallis grass) staggers, Bermuda grass staggers, and corn staggers. Hyperexcitability and muscle tremors (which are enhanced by disturbing the animal) characterize the disease syndromes. Affected cattle have a stiff, stilted gait, ataxia, and may fall. A down animal may not get up unless left undisturbed for some time. Clinical signs include twitching of shoulder and flank muscles, head tremors, and an inability to stand or walk. Animals may become debilitated (limb injuries) and death from dehydration can occur.
- In all grass staggers syndromes, hazard increases with plant maturity and is greatest in later summer and fall particularly as a result of rainy, humid weather.

Paspalum or Dallis Grass Staggers

Sources

- Paspalum staggers has been associated with Argentina Bahia grass and brown-seed paspalum in addition to Dallis grass (all *Paspalum* spp.).
- The syndrome has been associated with heavy ergot infection of Dallis grass heads. Both the sclerotial stage and the honeydew stage may induce the toxicosis.
- Dallis grass grows primarily fom New Jersey south to Tennessee and Florida, west to Texas and California. Close grazing or mowing is recommended to prevent ingestion of ergot sclerotia in the mature seed heads. It is, however, also cut for hay.
- Paspalum staggers has been reported primarily in cattle and occasionally in sheep and horses in New Zealand, S. Africa, Australia, the USA, Portugal and Italy.
- *Claviceps paspali* grows on Dallis grass especially and generally produces little ergot alkaloid, but may produce significant tremorgens, namely paspalitrems.
- *Claviceps purpurea* generally produces ergot alkaloids ± a small amount of tremorgen.

Poisonous Principles

- Two of the tremorgens produced by *C. paspali* are paspalitrems A and B.
- Honeydew stage-toxicity.
  - Before the sclerotia are formed in the mature seed head, the infected flower heads are in the honeydew stage.
  - These may be up to 30 - 50% as toxic as the sclerotia.
- Lysergic acid related (ergot) alkaloids are present in low concentrations in ergotized Dallas grass, but these are apparently not responsible for the clinical neurology effects.
- Instead, the agents probably responsible are the tremorgens in the ergot sclerotia, which are roughly 1/30 as potent as penitrem A.
- When ergot alkaloids are administered with the tremorgens no difference is seen from animals receiving tremorgens alone.
- When the ergot sclerotia were force-fed to a 20 kg lamb at a high, 135 gm, single dose, it developed severe head and leg tremors the first day. The signs increased, and within 2 days the lamb was laterally recumbent, thrashing its limbs; and it died on the 3rd day.
- When 45 gm given daily for 3 days, a second lamb showed similar but less severe signs becoming recumbent on its sternum within 1 week of initial dosing. Over 2 weeks there was little change--tremors became severe and it was unable to stand. Its appetite remained good but its physical condition restricted its intake. It was assisted to and supported on its feet frequently during the 4th week at the end of which it was able to stand a few minutes. Thereafter, it gradually recovered over several weeks.
- When lambs were dosed over 6 - 8 consecutive days, mild head tremors were present at 24 hours after the 1st dose. Signs increased over 72 hours and incoordination of movements was noticeable after being driven. Responses were similar at 4 and 5 days. At 6 days, one showed severe tremors and rocked unsteadily on its feet and, therefore, they received no more ergot material. One lamb collapsed and thrashed about on the 7th day after a dog chased them.
- On days 8 - 12 all showed marked head and limb tremors and incoordinated limb movements when moved. When chased for a short distance, all developed short, stiff, leg movements, collapsed, and rolled on their sides. After several minutes on the ground, the lambs walked away unsteadily with hindquarters swaying and with general shaking of the body. From this state all the sheep made a gradual but complete recovery over 14 - 20 days.

- Cattle are more sensitive than sheep but recover faster. Cattle are also more prone to eat seed heads (includes sclerotia) while sheep favor the basal leafy material.
- When four steers were orally dosed with ergotized paspalum seed, head tremors became apparent within 24 hours. By 48 hours neck tremors and head nodding movements appeared. On the third day marked tremors of shoulders and hindquarter muscle groups were present. Incoordination, swaying, stumbling, and commonly collapse occurred. All signs increased when driven. On cessation of dosing, cattle got better each day. Recovery was complete in 4 - 6 days. Signs regressed in the reverse order of appearance. A dose of paspalum ergot greater than 1 gm/kg/day was enough to produce severe staggers in cattle.
- Lysergic acid alkaloids.
    - When sheep were given 3 mg D-lysergic acid hydroxyethylamide, the signs of Dallis grass staggers were not reproduced. Instead, the sheep almost immediately had lip licking movements and tail wagging, and they walked in a backwards direction. Frequently the hindquarters sagged somewhat, then the stance was corrected with a sudden jerk. No head or body tremors were seen but the respiratory rate was increased. The response reached a peak within 1 hour of injection and then declined until the sheep were normal within 5 hours. Thus, LSD effects are **not** those of Dallis grass staggers.

Cattle and Sheep - Summary of Signs of Paspalum Staggers

- Tremors either confined to the head or extending over the whole body, and incoordination.
- Severely affected animals may show only mild tremors when undisturbed, but when forced to run quickly develop incoordination-marked tremors and temporary collapse.
- Cattle and sheep typically move their hind legs in unison.

Ryegrass Staggers

- Ryegrass staggers is a significant problem affecting sheep, cattle, and sometimes horses in New Zealand, Australia, and possibly the Southeast USA.
- Toxicosis occurs primarily on perennial ryegrass (*Lolium perenne*) pastures that are eaten down low, and are dry. Sheep more commonly poisoned since they graze lower.
- Poisoning also associated with horses fed a pelleted ration that had perennial ryegrass hay presumably from Oregon as the primary ingredient.
- The organism now believed to produce to principal toxin that accounts for the signs of ryegrass staggers, lolitrem B, is produced by the endophytic fungus, *Acremonium lolil*.
- Previously suggested causes include Penitrem A and other tremorgens such as verruculogen and fumitremorgen B.
- *Aspergillus caespitosus* as well as *Penicillium piscarum* (isolated from a ryegrass pasture after a staggers episode in New Zealand) produced the latter two of these tremorgens.

Clinical Signs and Lesions

- **Horse**.
    - Mild excitability, spastic ataxia, hypermetria, tetany (severe cases).
    - Elevated lumbosacral cerebral spinal fluid protein concentration 76 - 138 mg/dl. Normal values 70 mg/dl.
    - *Penicillium cyclopium* identified in ryegrass strain.
- Animals often appear normal at rest. When incited to move, stiff spastic gait, muscle spasms, occasionally tetanic seizures.
- Some animals with ryegrass staggers may have lesions in cerebellar purkinje cells.

Corn Staggers

- May be seen with ingestion of corn silage.
- Especially associated with consumption (generally by cattle) of lodged (knocked down) corn.
- Spores of *A. flavus* and the tremorgen aflatrem have been implicated. It is likely that other *A. flavus*-produced toxins such as aflatoxins and cyclopiazonic acid may cause hepatic and digestive problems in some outbreaks.

Penicillium Martensii on Crabgrass also Produces a Tremorgen

- This toxin causes trembles, spastic legs, and some blindness.
- A similar syndrome has been experimentally reproduced in mice.

Note: *Claviceps paspali*, *Aspergillus* sp. and *Penicillium* sp. are the principal organisms known to produce tremorgens at the present time.

Key Features

- Moldy cheese, cream cheese, walnuts, refrigerator foods or occasionally grains
- Ergotized grain or Dallis grass, possible endophytic fungus in ryegrass.
- Fine muscle tremors, more severe tremors, hypermetria, excitation, seizures, deaths. Signs worse after stimulation. Hopping in large animals and with time weakness and paralysis.
- Signs may persist for days possibly up to weeks.
- Dallis grass staggers, cattle more sensitive.
- Signs in cattle usually disappear after 2 - 4 days on an uncontaminated diet.
- Treatment of acute toxicosis-terminate exposure and consider symptomatic and especially supportive care (herd feeding and watering may be essential); activated charcoal and saline cathartic.

Bermuda Staggers (Bermuda Grass Tremors)

- First reported to affect cattle in 1951.
- Affects animals in large areas of the southern USA.
- Causative toxin(s) has **not** been identified.
- 3 syndromes have been associated with ingestion of Bermuda grass:
    - Tremors and/or posterior paralysis that may be exercise-associated with consumption of hay.
    - Hepatogenous photosensitization, icterus.
    - Pulmonary edema and emphysema associated with consumption of green grass in spring.

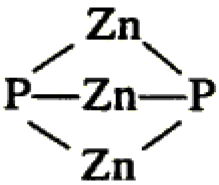
Zinc Phosphide and Aluminum Phosphide

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Zinc phosphide (rodenticide)	All species, esp. dogs	Minutes to hours (neurologic or respiratory effects). Days (liver failure)	Neurologic signs: 1 to 2 days; often lethal Liver damage: days to permanent	
Aluminum phosphide (Fumigant)	All species	Minutes to hours (neurologic or respiratory effects). Days (liver failure)	Neurologic signs: 1 to 2 days; often lethal Liver damage: days to permanent	

Sources

- Zinc phosphide is a dull, grayish-black powder used mainly as a rodenticide and for killing moles. Products: Zinc Phosphide, Kilrat, Rumutan.
- Zinc phosphide, or occasionally aluminum phosphide, may be used in baits of bread, buns, soaked wheat, damp rolled oats, or sugar at concentrations of 2 - 5%.
- Aluminum phosphide is used as a grain fumigant for insect and rodent control and in dusts for insect control.
- Zinc phosphide is unstable in water or acid, but is stable for about 2 weeks under average climatic conditions. Can be stable for long time periods if kept dry.
- Aluminum phosphide degrades more readily than zinc phosphide.
- Either compounds degrade to reactive (toxic) phosphine gas which accounts for much of the toxicity and smells like garlic or rotten fish.

Zinc Phosphide



Toxicity

- Lethal doses cattle, sheep, pigs, goats, dogs, cats between 20 - 50 mg/kg.
- Animals poisoned by feeding directly on bait or relay toxicosis associated with eating tissues of zinc phosphide-poisoned animals.

Mechanism

- Food in the stomach increases HCl production which greatly increases the breakdown to toxic phosphine (PH_3) gas which induces serious acute effects due to enteric and pulmonary irritation. $Zn_3P_2 + 6H_2O$ ö $3Zn(OH)_2 + 2PH_3$.
- CNS effects are due to an unknown mechanism but acidosis and hypocalcemia may occur.
- Both phosphine and intact zinc phosphide are absorbed from the GI tract. The phosphine is believed to cause the majority of acute signs, while the intact phosphide may cause hepatic and renal damage later.

Signs

- Zinc phosphide causes emesis frequently in nonrodent species and, because of this effect, fatal poisoning is not a consistent sequel to ingestion. A few preparations have added tartar emetic to increase vomiting.
- Onset of clinical signs usually occurs from 15 minutes to 4 hours after ingestion, but may be delayed for up to 18 hours.
- Large doses may cause death within 3 - 5 hours.
- Severely affected animals rarely live longer than 48 hours.
- The vomitus of zinc phosphide-poisoned animals often contains dark blood.
- Dogs may show lateral recumbency with whole body tremors and salivation. May proceed into "running fits" and repeated jerking of the head. Terminal exhaustion may occur.
    - Anorexia, lethargy, and rapid deep breathing which often becomes wheezy or "clicky" sounding.
    - Abdominal pain, ataxia, weakness, and recumbency may follow.
    - Acidosis is prominent, and there may be hypocalcemia, terminal hypoxia, gasping, and struggling.
    - Hyperesthesia and sometimes seizures may be seen, and in some dogs these may closely resemble strychnine convulsions.
    - Hepatic and renal damage often may be detected 5 - 14 days later.
    - Acetylene (garlic, rotten fish) odor on breath.
- Abdominal pain, colic in horses, and bloat in cattle.

Lesions

- Opening the stomach will reveal a characteristic acetylene odor and possibly evidence of gastritis (may be severe).
- Nonspecific postmortem findings.
- The lungs are often markedly congested and may have interlobular edema, pleural effusion, subpleural hemorrhages also noted.
- Acutely affected animals have extreme congestion of the liver and kidney.
- Myocardial degeneration sometimes may occur.
- Pale yellow mottling of liver may appear in subacute cases.
- On histopathology, there is fatty change and congestion of the liver and kidneys. Also, there may be renal tubular degeneration, hyaline change, and necrosis.

Diagnosis

- Tentative diagnosis based on compatible clinical signs, an acetylene odor to the breath, and opportunity for or, better, evidence of exposure to zinc phosphide. Phosphine gas rapidly dissipates.
- Frozen vomitus or gastric lavage fluid may be submitted in an attempt to obtain confirmation (phosphine gas identified for zinc or aluminum phosphide analyses). Air-tight containers required, keep samples frozen.
- Rapid freezing (and care to maintain the frozen state in transit) of stomach contents, liver, and kidney increases the probability that laboratory analysis for phosphine gas may turn out to be worthwhile (be sure laboratory has capability to run).
- With phosphine method, false negatives may be encountered.
- In some cases, concentrations of zinc in serum, liver, and kidney may be elevated but these assays are more difficult to interpret. Because of the use of zinc stearate to coat rubber, serum samples for analysis of zinc must be drawn in all glass or all plastic syringes (no rubber), and all glass or all plastic vials (no rubber stoppers) must be used for transport.

Treatment

- The gastrointestinal contents should be evacuated by emesis in suitable species following administration of aluminum plus magnesium hydroxide gel (e.g., Maalox®) (Empirically recommended [rather than oral bicarbonate] to decrease phosphine release.). Activated charcoal orally, preferably mixed with sorbitol.
- Respiratory failure may necessitate administration of 100% humidified oxygen or possibly artificial respiration via a ventilator with positive and expiratory pressure (PEEP).
- Metabolic acidosis is corrected by IV administration of sodium bicarbonate (slow, in fluids).
- Fluids may be administered IV and corticosteroids may be needed to help alleviate shock.
- B-vitamins and dextrose may be used for possible hepatic injury along with appropriate dietary therapy.
- Seizures may be controlled with diazepam or, if it fails, phenobarbital or, if it fails, anesthesia induced with pentobarbital.

Key Features

- Zinc or aluminum phosphide exposure.
- Rodenticide, fumigant, occasionally insecticide.
- Phosphine release-cause of acute effects, acetylene (fish, garlic) odor.
- Gastrointestinal upset.
- Respiratory and/or neurologic signs.
- Delayed liver or kidney failure.
- Diagnosis-difficult, try GI tract contents (freeze rapidly, ship in air-tight container), serum.
- Treatment: aluminum or magnesium hydroxide gel, evacuate GI tract, adsorbent, supportive, and symptomatic.

Cicuta spp. - Water Hemlocks

Cicuta maculata, Cicuta douglasii

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. ruminants, swine	Minutes	Hours; often lethal	

Description

- Native perennial herb.
- 2 - 10 feet tall.
- Stem stout, hollow, often purple streaked.
- Base of stem hollow below ground with horizontal plates crossing hollow central cavity. Contains highly poisonous resinous material.

- Leaves alternate, sheath stem.
    - 2 - 3 times pinnately compound.
- Flowers small white in compound umbles.
- Technical details used to separate from harmless genera like *Angelica* and *Osmorhiza*. (Consult with plant taxonomists-weed specialists, etc.)

Habitat

- Wet, rich soil.
- Along ditches, low meadows, flood plains, swampy areas, stream beds, marshes.
- 8 species in USA; *C. maculata* most important in eastern half of country.

Toxic Principle and Toxicity

- Cicutoxin-a long-chain highly unsaturated diol ($C_{17}H_{22}O_2$).
    - Thick, yellow liquid with a carrot-like odor (also smells like raw parsnips). Especially in roots and base of stem (tubers) at or below ground surface. Tubers are toxic all year.
    - Young leaves are nearly as toxic as roots, but mature leaves in summer and autumn have been consumed causing no problem. Animals tolerate low amounts without displaying clinical signs.
    - Among the most toxic plants in USA.
- 2 oz of tubers can kill a sheep. 8 - 10 oz of mature plant can kill a cow.

Susceptible Species

- Livestock and humans.
    - Expecially from eating tubers, base of stem, young leaves.
        - Tubers and liquid containing cicutoxin therein may be consumed, especially when eating lower stems early in the year when the soil is moist and soft.
- Cattle.
    - Toxicosis reported from eating plant or drinking water in puddles with trampled plant material present.
    - Usually not a problem in hay unless roots are included (unlikely).

Signs

- Cattle, sheep, other species affected: swine less often affected, possibly due to vomiting.
- Rapid onset-begins 30 minutes after ingestion; death within 45 - 60 minutes of ingestion.
- Peracute, violent course.
- Salivation.
- Muscle twitching.
- Chomping of jaws.
- Grinding of teeth.
- Appear painful.
- Muscle spasms.
- Convulsions.
- May be knocked off feet by seizures.
- Then running fits and convulsions continue.
- Coma.
- Death due to respiratory paralysis.
- In poisoned human beings, electroencephalographic abnormalities and occasional anxiety neurosis persisted at 3 month after exposure.

Lesions

- Are preventable with treatment of poisoned animals (possible due to exertion and hypoxia).
- In untreated animals include: skeletal and myocardial degeneration.

Clinical Pathology

Elevated muscle enzymes (LDH, AST, CK) may occur (variable).

Treatment

- Usually too late.
- Usually if animal lives 2 hours, it is likely to survive.
- Control spasms, seizures with sodium pentobarbital.
- Assist (artificial) respiration if necessary and possible.
- Activated charcoal and saline cathartic if hydration near normal; if not give adequate fluids then give saline cathartic.

Corydalis caseana - Fitweed

C. aurea - Golden Corydalis
C. sempervirens - Pale Corydalis
C. flavula

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. sheep	Minutes	Hours to 2 days; potentially lethal	

Family - Fumariaceae (Fumitory Family)

Description

Biennial or weak perennial, succulent, bushy, spreading branches, grows up to 3 feet tall, fleshy top root, pinnately decompound leaves. Fragrant, up to 3 inches long racemes of creamy white, spurred flowers, each about 3/4 inches long at ends of branches. Flowers may be tipped with purple.

Habitat

- ***C. caseana***

  Sierra Nevada Mountains of California. Shaded canyons in summer ranges; moist places along streams and near water between 1600 and 2200 meter elevations.

- ***C.aurea***

  Eastern North America and Rocky Mountains. Open woods and recent clearings on stony, calcareous soils; disturbed areas, along streams, sandy soil.

- ***C. sempervivens***

  Northern USA and parts of Canada. Open woods, recent clearings, burned-over areas and rocky banks.

- Poisonings primarily in mountains of Rocky Mountain region and Virginia.

Toxic Principles

Isoquinoline alkaloids.

Susceptible Species

Sheep seem to relish the plant, cattle sometimes also affected. Sheep are apparently more susceptible than cattle and horses.

Toxicity

- Considerable quantities must be consumed: 5% of the animal's weight is potentially lethal to sheep and 2% may produce clinical toxicosis.
- Plant rarely abundant.
- Plant is toxic in all stages of growth; summer (July to September) most dangerous months.

Signs

- **Sheep**.
  - Rapid onset.
  - Rapid breathing and increased heart rate.
  - Ataxia and fall into clonic seizures, which occur intermittently.
  - Animals weaken and respiration and cardiovascular functions become depressed.
  - Twitching of facial muscles, running fits.
  - Sharp external stimulus during seizures may provoke sudden rigidity.
  - Scouring is common.
  - Dyspnea in some.
  - Bleating and other vocalization is common.
  - Characteristic biting (chewing) movements.
  - After several convulsions, death may occur (usually in less than 24 hours).
  - Affected animals may make a rapid, uneventful recovery.

Lesions

Nonspecific.

Treatment

- Remove access to plant.
- Activated charcoal and if hydration is adequate or restored to near normal, a saline cathartic may be administered.
- Symptomatic and supportive care.

Prevention

Supplemental feeding may reduce consumption to subtoxic amounts.

Milkweeds (*Asclepias*)

Asclepias subverticulatta and ***A. fascicularis*** - whorled milkweeds.
A. eriocarpa - a broad leaf milkweed of California.
A. syriaca - common milkweed.
A. incarnata - swamp milkweed.

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Herbivores, esp. sheep	Minutes to hours	Hours to days; potentially lethal	

Description

- Native perennial herbs.
- Sap milky, hence the name milkweed.
- **Note** - Other common poisonous plants with milky sap include the *Euphorbia* spp. (spurges) and *Apocynum* spp. (dogbane). **Note** - not all plants with milky sap are poisonous.
- Leaves opposite or whorled.
- Numerous seeds with tufts of silk in tear drop shaped pods.
- May be free standing or vines may cling to fences.

- Broad leaf and narrow leaf varieties exist. Whorled milkweeds have narrow leaves. Narrow leafed milkweeks tend to be of higher toxicity.
- Flower color varies with species. Most flowers are white, some purple, others range from white to red or orange.
- Become more common as a result of heavy grazing.
- Some are more common on sandy soils.
- Especially in western Midwest, Rocky Mountain areas, and southwestern California and Baja.

Toxic Principle

- A "**resinoid**" exists at least in the tops of the plants which has been named galitoxin. "Resinoid" is defined as a substance resembling a **resin**. A resin is defined as a solid or semisolid organic substance of vegetable or synthetic origin that is insoluble in water but readily dissolves in alcohol, ether, and volatile oils.
- Toxic dose almost same as lethal dose.
- Taste less objectionable when dried, but toxic principle is retained.
- Roots and shoots are also toxic.
- Some western species contain cardenolides (cardioglycosides). Cardenolides are the main cause of fatalities.

Toxicity

***Asclepias* spp.**	**Common Name**	**% Body Weight of Green Plant causing Fatalities**
A. labriformis	Labriform milkweed	0.05 - 0.20
A. fasicularis	Whorled milkweed	.20
A. latifolia	Broadleaf milkweed	1.00

Poisoning

- Only when good forage is inadequate.
- Frost decreases toxicity.

Signs

- Sheep affected most; occasionally in horses, cattle, goats, fowl.
- Natural cases of milkweed poisoning, animals are usually found dead or in lateral recumbency within 24 hours of consuming a toxic quantity of the plant.
- Clinical signs can develop within 2 hours of ingestion and can continue for hours or days.
- Pulse initially slow and strong then rapid and weak.
- Hyperthermia, bloat.
- Whorled milkweeds (*A. subverticullata* and *A. fascicularis*) produce CNS signs.
    - Convulsions - usually preceded by severe depression, weakness, muscle tremors, ataxia, dyspnea.
    - Convulsions that occur are tetanic in nature, repeatedly occur.
    - Coma.
    - Elevated temperature.
    - Death due to respiratory failure, tachyarrhythmias.
    - Congestion - internal organs - CNS.
- *A. eriocarpa* - one type of broad leaf milkweed - dry soils - California.
    - GI signs; gastroenteritis, bloat in ruminants, crop impaction in birds.
    - Subnormal temperature.

    - Prostration.
- Cardiac glycoside containing milkweeds may cause digestive tract upset followed by bradyarrhythmias and/or tachyarrhythmias.

Pathology

- No specific lesions.
- Congestion of lungs, liver, kidney frequent. Mild to severe hemorrhagic gastroenteritis with broadleaf varieties.

Treatment

- Activated charcoal. Rumenotomy beneficial in early stages of poisoning.
- Symptomatic - control seizures.
    - Assist respiration.
    - Good diet.
- If signs of cardioglycoside toxicosis exist manage as cardioglycoside overdose (see toxins affecting the heart).
- Chloral hydrate reportedly is effective in relaxing sheep in the convulsive stages and allows time for recovery.

Milkweed Family, *Asclepiadaceae*

Oligomeris - Desert Spike

***Oligomeris linifolia* - Desert Spike** - (Mignonette Family)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants Associated with Stimulation or Seizures
Cattle	Days to weeks	Unknown; potentially lethal	

Description

Annual, cool season (fall and winter), herb.

Habitat

- Native to the Rio Grande Valley and Trans Pecos area of Texas and on to California, including Northern Mexico, low elevations.
- Poisoning may be more common in years of high rainfall, which seems to promote the growth of this plant.

Susceptible Species

Poisoning has been documented in cattle.

Toxicity

Low levels fed for 1 month caused mild depression and only very slight weight loss. At 5 - 20 g/kg fed for 26 days, marked "CNS signs" and 19% weight loss occurred. At 5 - 10 g/kg fed for 25 days, severe "CNS signs", seizures and 20% weight loss occurred. At 10 - 18 g/kg fed for 11 1/2 days, with the higher amounts being fed the last few days, severe CNS signs, mania, stupor, and pulmonary emphysema were seen.

Signs

- Mild depression
- Salivation
- Ear twitching or exaggerated frequency of ear movement
- Blinking
- Increased tail movement
- Tremors
- Continual walking
- Stimulated appearance
- Apparent hallucinations
- Facial spasms
- Epileptiform seizures
- May see mild increase in glucose and increase in CPK
- Walk into walls
- Weakness
- Recumbency
- Stupor
- Nystagmus
- Dyspnea
- Death
- Goose-stepping
- Wide stance
- Chewing fits

Lesions

No gross or histologic lesions.

Treatment

- Rumen lavage has been demonstrated to be of major benefit in alleviating and shortening the duration of toxicosis.
- Activated charcoal is recommended when lavage is impractical (as often is the case).
- Tube feeding can make a major difference in the survival rate as well.

Toxicants with Mixed Effects on the Central Nervous System

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Lead Toxicosis

(Plumbism)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Most species, especially dogs, horses, cattle, waterfowl. Swine resistant.	Hours to months	Days to permanent damage; often lethal	

Sources Usually Involved with Small Animals

- Lead paint, especially paint chips lost during remodelling. Lead is still commonly found in some artist's paints.
- Lead objects, especially a concern with psittacine birds, dogs:
  - Toys, drapery weights, sinkers, solder, foil from top of wine bottles.
- Plumbing materials.
- Lead shot in tissues (usually does not cause lead toxicosis).
- Tile, linoleum.
- Improperly glazed bowls.
- Leaded gasoline (contains the organolead compound, tetraethyl lead, which is highly absorbed by all routes). Also burning of tetraethyl lead produces particulate lead in the exhaust of engines burning regular [leaded] gasoline). Leaded gasoline was banned years ago in the U.S.A., however, it is still in use in some countries.
- Soil near roads and urban buildings.
- Soil near lead smelters.
- Absorption of lead from soil presumably follows ingestion associated with grooming.

Sources Usually Involved With Large Animals

- Batteries in pastures, broken in feed mixers, etc.
- Roofing felt.
- Motor oil from engines that burn regular gasoline (no longer a likely source in the USA).
- Grease if it contains lead.
- Lead paint (licked from the walls of barns, in paint cans, etc.).
- Lead smelters-effluent onto forage; also, some uptake by plants.
- Lead mine tailings.
- **Note**: With lead arsenate pesticides; signs and lesions of poisoning relate **much more to arsenic** than to lead.

Sources Water Fowl

- Consumption of lead shot or lead sinkers.
- Lead shot was recently banned for waterfowl but is still used for upland game. Lead shot availability to waterfowl via sediments depends in large measure on the nature of the substrate and the tendency for the pellets to penetrate into the deeper layers.

Susceptibility

- Young more susceptible: absorb greater fraction of ingested amount.
- Dogs, horses, cattle, and waterfowl are all poisoned comparatively often.
- Horses may be even more sensitive than cattle.
- Cats are probably of intermediate sensitivity but are infrequently poisoned.

- Sheep are probably of intermediate sensitivity.
- Swine, goats, and chickens are comparatively tolerant.

Toxicity

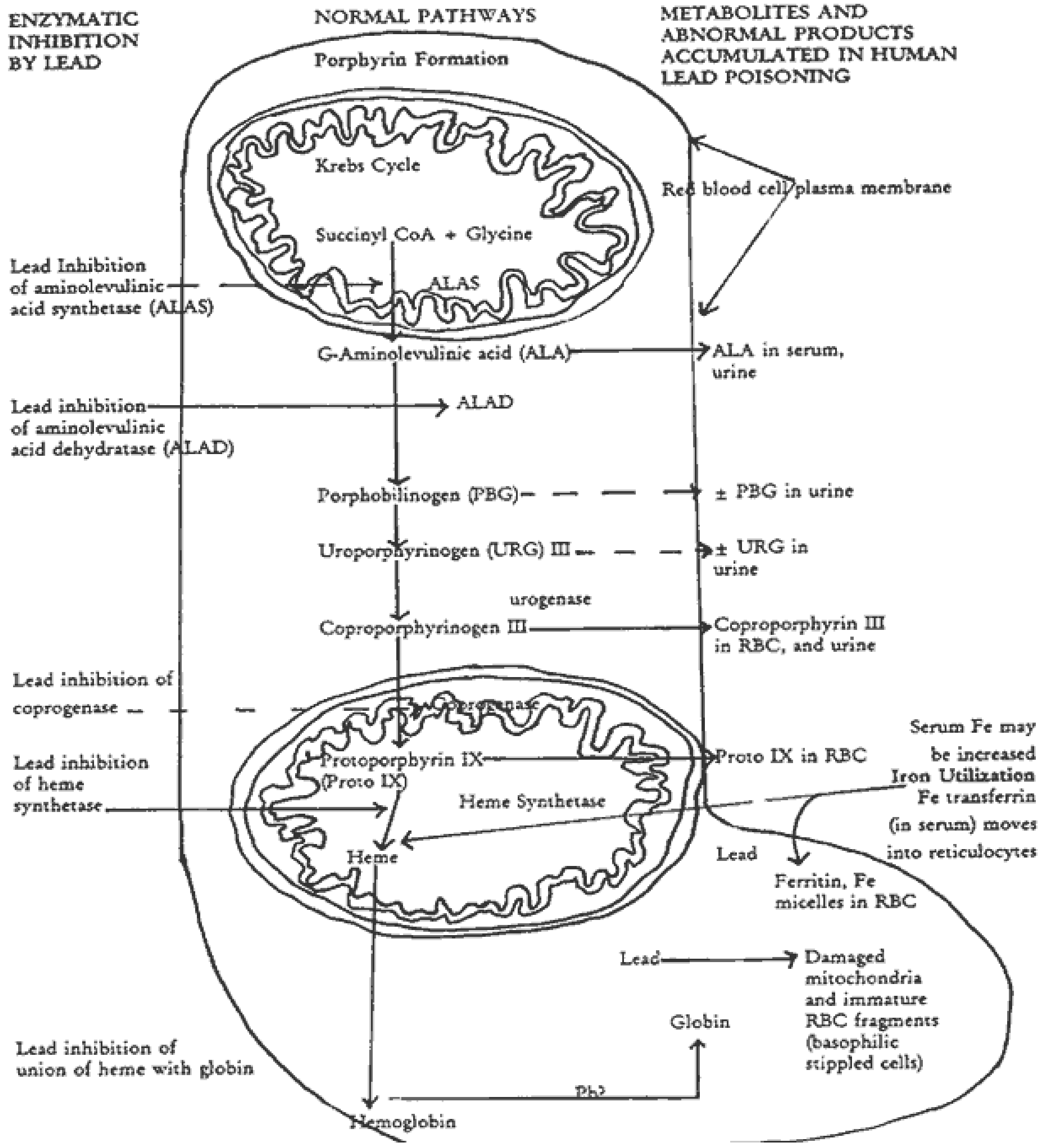
- Toxicosis is usually due to acute exposure, but can result from repeated exposure with a gradually increased buildup of lead in the body.
- Acute single lethal dose of lead ranged from 400 - 600 mg/kg in calves and 600 - 800 mg/kg in adults. Lead is toxic at 6 - 7 mg/kg when eaten daily by cattle.
- Ingestion of 1 - 3 lead shotgun pellets can be lethal to waterfowl. Lead shot tends to remain in gizzard.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Most common route of exposure is oral ingestion of lead. However, inhaled lead particles are cleared by mucociliary action and then swallowed.
- A small amount (1 - 2%) of the lead ingested is absorbed. Most of the remainder is excreted in feces as insoluble lead complexes.
- A greater degree of absorption occurs in the young, especially when calcium deficient.
- Absorption depends in part on the surface area, therefore finely divided lead as occurs in used motor oil is more toxic.
- Lead crosses the placenta and can enter milk.
- In cattle, ingested objects containing lead may settle and be retained in reticulum allowing absorption of lead over an extended period of time.
- Inorganic lead is not absorbed through intact skin, but tetraethyl lead, as in regular (leaded) gasoline is readily absorbed.
- Lead is slowly excreted in untreated animals; and is excreted predominately via the bile. Enterohepatic circulation not known. Urine excretion is minimal unless chelation therapy is administered.

Mechanisms and Clinical Pathologic Effects

- Lead affects multiple tissues, especially the gastrointestinal tract and nervous system.
- Interferes with thiol (-SH containing) enzymes.
- Lead may replace zinc in some enzymes.
- Cerebral edema and neuronal damage centrally, demyelination and reduced nerve conduction velocity peripherally.
- At very high concentrations, lead may interfere with GABA mediation by lowering GABA concentrations at inhibitory interneuron junctions in the CNS.
    - At high concentrations inhibits these inhibitory interneurons.
- Lead can cause anemia:
    - Increased red cell fragility.
    - Depression of bone marrow (several enzymes are affected).
        - Interferes with function of delta aminolevulinic acid (ALA) dehydratase (an enzyme functioning in heme synthesis), therefore, a large increase is seen in delta-ALA in the plasma and urine of lead poisoned animals. Other heavy metals, e.g., Zn, Cu, Hg, also depress this activity in circulating blood but not to the same degree as lead. Alcohol and possibly ethylene glycol can also depress this activity.
        - Lead also interferes with the incorporation of iron into the heme molecule via inhibition of heme synthetase. Therefore, one sees an increase in protoporphyrin.
        - Inhibition of the enzyme nucleotidase is thought to be responsible for basophilic stippling and increased fragility of RBCs.
        - Zinc protoporphyrin increases in lead poisoning. Apparently, the failure of heme synthetase to insert iron atoms leaves protoporphyrin free to chelate endogenous zinc atoms. This indicates a chronic metabolic effect of lead on newly produced RBCs. Zinc protoporphyrin will generally remain normal for first 1 - 2 weeks following lead exposure.
- With chronic or subchronic toxicosis may see nucleated red blood cells and increased numbers of cells with basophilic stippling present. This occurs most often in dogs and is often present in the face of normal or only slightly reduced red blood cell counts and hemoglobin concentrations. Basophilic stippling can be normal in ruminants and is therefore not considered to be a diagnostic feature.


ENZYMATIC INHIBITION BY LEAD
NORMAL PATHWAYS
METABOLITES AND ABNORMAL PRODUCTS ACCUMULATED IN HUMAN LEAD POISONING
Porphyrin Formation
Krebs Cycle
Red blood cell/plasma membrane
Succinyl CoA + Glycine
Lead Inhibition of aminolevulinic acid synthetase (ALAS)
ALAS
G-Aminolevulinic acid (ALA)
ALA in serum, urine
Lead inhibition of aminolevulinic acid dehydratase (ALAD)
ALAD
Porphobilinogen (PBG)
± PBG in urine
Uroporphyrinogen (URG) III
± URG in urine
urogenase
Coproporphyrinogen III
Coproporphyrin III in RBC, and urine
Lead inhibition of coprogenase
Coprogenase
Serum Fe may be increased
Lead inhibition of heme synthetase
Protoporphyrin IX (Proto IX)
Proto IX in RBC
Iron Utilization
Fe transferrin (in serum) moves into reticulocytes
Heme Synthetase
Heme
Lead
Ferritin, Fe micelles in RBC
Lead
Damaged mitochondria and immature RBC fragments (basophilic stippled cells)
Globin
Lead inhibition of union of heme with globin
Pb?
Hemoglobin

Mechanism of Action not completely understood

Signs

- **Neurologic effects**.
  - Nervous system signs often predominate.
  - Blindness. Swelling of optic disk. Iridocyclitis.
  - EEGs indicative of increased irritability.
  - Hysteria, chomping, seizures, muscle spasms, opisthotonus.
  - Retardation in children, sometimes animals.
  - Circling.
  - Pushing against objects (head pressing).
  - Ataxia.
  - Cattle - rhythmic bobbing of the head, twitching of the ears, exaggerated blinking, fine muscle tremors, marked excitement or seizures (bad prognostic sign).
  - Segmental demyelination interferes with nerve impulse conductance in peripheral nerves. Signs of peripheral nerve involvement are associated with chronic lead poisoning, can be

important, especially in the horse. Motor nerves primarily affected with little sensory perception loss. Horse:
        - Paresis of lower lip, laryngeal paresis, pharyngeal paresis, and rectal sphincter paresis.
        - Regurgitation of water from nose when horse drinks.
- **Gastrointestinal tract**.
    - Mucosal damage, abdominal distress, tucked abdomen.
    - Anorexia, vomiting.
    - Constipation, then diarrhea, colic.
    - Cattle - rumen motility reduced or abolished, grinding of teeth.
- **Respiratory**.
    - Inspiratory dyspnea in horses occurs due to paralysis of recurrent laryngeal nerve, "roarers".
    - Death can occur from respiratory paralysis during convulsions.
- **Immune system**.
    - Somewhat immunosuppressive, even with amounts in the body insufficient to cause clinical effects.
- **Reproductive**.
    - Crosses placenta and affects fetus: can cause abortion, resorption, and sterility.
    - Some in milk, increased tendency of young animals (and people) to absorb lead.
- **Psittacine birds.**
    - Clinical signs often vague. Nonspecific gastrointestinal, renal, and neurologic dysfunction. Often acute onset.
    - Depression, weakness, anorexia, regurgitation, polyuria, greenish-black diarrhea, ataxia, headtilt, blindness, circling, and convulsion have been reported.
    - Suspect if hemoglobinuria and CNS abnormalities are present.
- **Waterfowl signs.**
    - Clinical signs of toxicosis in wildlife are frequently not observed.
    - Animals are not provided with a sheltered existence and human monitoring.
    - Generally just see decreased numbers in an affected population.
    - May have increased predation, starvation, etc., in a sublethally poisoned population of waterfowl.

Lesions

- Lead objects, paint, or used motor oil in the gastrointestinal tract in some cases.
- Mild gastritis or enteritis.
- Esophageal dilatation in some dogs.
- Pale liver, possible to see evidence of centrilobular degeneration. May have acid-fast intranuclear inclusions in hepatocytes.
- Muscle may also be pale.
- Kidneys may be acutely hyperemic or hemorrhagic; with chronic toxicosis possible to see fibrosis. Do not rule out lead toxicosis because of the absence of renal lesions. Degeneration and necrosis and sometimes prominent, acid-fast intranuclear inclusions may occcur in the renal tubular epithelial cells. It can cause a degree of renal failure, although this is not usually a primary finding.
- May see edema, swelling, increased prominence of vessels in the brain.
    - Capillary damage in the CNS. Collapse of small arterioles.

Diagnosis

Antemortem

- Blood lead (whole blood: heparinized or EDTA tubes).
    - 0.6 ppm or greater is diagnostic (often 1 to 1.2 ppm).
    - 0.35 ppm or greater with signs and especially with confirmatory tests (such as delta ALA or fecal lead) is also diagnostic.
    - Lead is carried on the red cell, 90% of circulating lead is bound to erythrocytes. Therefore, serum lead is **not** routinely used and is not readily interpretable.
    - Blood lead concentrations are a valuable indicator of exposure but they do not indicate the length of exposure or total amount of lead deposited in the body. They do not correlate extremely well with the severity of clinical signs.
    - In chronic exposures (man), there can be a high percentage (approximately 30%) of false negatives.

- Nucleated RBCs or basophilic stippling (in dogs, cat, horse) is suggestive but, if not present, does not rule out lead toxicosis.
- X-ray abdomen or reticulum of ruminants when possible.
    - Positive findings can help to rule in, negative X-ray findings do not rule out lead poisoning.
- X-ray epiphyseal plate.
    - Infrequently see lead line, even in lead poisoned dogs.
- Serum ALA dehydratase inhibition and erythrocyte protoporphyrin assays are highly sensitive tests for exposure to, and an indication of a possible effect of lead. They are not a substitute for blood lead assay which confirms the presence of the metal as a specific cause.
- Urine increase in delta ALA. Not as reliable as serum ALA dehydratase activity.
- Hair: shedding in animals decreases the value of lead analysis and hair is not as good an indicator of chronic exposure as in man.
- Fecal lead: 35 ppm is suspect.

Postmortem

- Liver and kidney. Renal cortex more reliable to assay than liver because kidney stores more lead.
    - 1 - 10 ppm; usually when see 10 ppm call conclusive toxicosis, with other supportive findings present, toxicologists may consider somewhat lower concentrations to be diagnostic.
- Characteristic lesions.

Differential Diagnosis

- Dog, cat: rabies, distemper, hepatitis, other heavy metal toxicoses.

Ruminants -	major DDx:	rabies, poliencephalomalacia, TEME, listeriosis.
	minor DDX:	hypomagnesemic tetany, nervous ketosis, hypovitaminosis A, nervous coccidiosis, mercury poisoning, meningitis, encephalitis, hepatoencephalopathy, organic insecticide poisoning.

Treatment

- Locate source and prevent further exposure.
- Remove remaining lead from digestive tract.
    - Saline cathartic.
        - Sodium sulfate or magnesium sulfate (0.5 mg/kg in a 10% solution in H_2O PO or by stomach tube).
        - Promotes evacuation, plus insoluble (poorly absorbable) lead sulfate is formed.
        - Gastric lavage (infrequently needed).
    - Surgery to remove large objects, particularly those not progressing through the GI tract.
        - X-ray to be sure removal was complete.
        - Rarely necessary to remove lead shot from tissue after gunshot, but if it is associated with high blood lead and clinical signs, and if other exposure has not occurred, removal may be needed.
- Ingested lead paint or lead in motor oil, etc., is usually not evident on x-rays.
- Flush and siphon lead pellets from gizzard or feed large amount of grit to expel pellets. Make sure proventriculus is not impacted.
- Removal of lead sinkers from the digestive tract may be essential for survival of large waterfowl such as swans.
- Some avian practitioners recommend feeding peanut butter in baby cereal to provide lubrication to aid in passage of lead foreign bodies.
- Chelation therapy.
    - Chelation: Binding in a nonionized, soluble complex (a chelate) that is excretable in the urine.
    - Orally administered chelation agents may enhance absorption of metals when present at elevated concentrations in the GI tract. They are, therefore, used (by this route) only after the metal has left the digestive tract.

    - CaEDTA = Ca disodium EDTA = Ca disodium ethylene diamine tetraacetate = Ca disodium versenate. Must use calcium EDTA: Na EDTA chelates calcium and, therefore, high doses can cause hypocalcemia.
    - Since CaEDTA can cause gastrointestinal and renal toxicosis, it is used judiciously in courses of therapy.
    - Clinical signs of experimentally induced CaEDTA toxicosis include anorexia, depression, diarrhea, and vomiting. Pathologic changes include intestinal congestion and hemorrhage, necrosis of the intestinal epithelium. Toxicity may be related to chelation of trace elements. **Note**: These clinical signs are similar to those reported for lead toxicosis in dog. Although less notable than in human patients, dogs and cattle may also experience necrotizing nephrosis in the proximal renal tubules, despite a normal BUN and creatinine. When present, renal signs tend to occur after the onset of gastrointestinal effects.
    - Zinc supplementation may reduce the gastrointestinal upset associated with CaEDTA therapy.
    - EDTA only slowly diffuses into the CNS. Does not penetrate red blood cells. Increases Pb excretion 20 - 50X. **Occasionally increases signs**, therefore, with severe toxicosis use BAL (British Anti-Lewisite, also called dimercaprol) first, then EDTA.
    - During second or subsequent courses of CaEDTA, it is a good idea to monitor urine Pb before and after CaEDTA to determine whether a large increase in urine lead occurs. If this occurs, it suggests that the lead may still be present at high concentrations in the tissues and therapy may need to be continued.
    - BAL removes lead directly from parenchymatous organs.
    - BAL - Reaches brain, recommended for small animals where severe CNS signs are present. Occasionally painful (is administered IM in oil).
    - BAL increases Pb excretion in urine, and especially via the bile, and removes Pb from red blood cells.
    - DMPS (2,3-dimercapto-1-propanesulfonic acid sodium salt) and DMSA mesodimercapto-succinic acid - Succimer® - a structural analog of BAL, show considerable promise as chelation agent. DMSA is available as a human product in 30 mg capsules. It is used in pet birds at 25 - 35 mg/kg PO BID 5 days a week for 3 - 5 weeks. DMSA appears to be a more rapid and effective chelator of lead, in birds, than Ca EDTA and is also less toxic (10).
    - Penicillamine is an orally administered chelation agent.
    - Penicillamine is sometimes used to follow up in-patient treatment as a home medication. One-week course or 2-week-long courses of penicillamine therapy separated by 1 week of rest.
    - In dogs, penicillamine is given at 10 - 15 mg/kg BID up to 55 mg/kg BID for 1 week or for 2 weeks (separated by 1 week interval). The drug should be given orally on an empty stomach. To minimize side effects such as anorexia, listlessness, and vomiting, the daily dose can be divided and given TID to QID. It should not be given to small animals with signs of vomiting, depression, anorexia, or marked neurological disorders. It is contraindicated when lead is still present in the gastrointestinal tract.
    - Penicillamine is often recommended in stubborn cases, where elevated blood lead persists.
    - Prior to metabolism, lead in tetraethyl lead (organic lead) is nonionic and therefore not accessible to chelation therapy.
- Chelation Therapy Dosage Regimens.
    - Horse/cattle - CaEDTA (6.6% solution) at 0.5 ml/lb (73 mg CaEDTA/kg) using slow IV administration in divided doses 2 - 3 times per day for 3 - 5 days. If necessary to treat more than 5 days (based on clinical signs, urine lead), a 2-day rest period is provided before the second 5-day course of therapy.
    - Dog - CaEDTA at 100 mg/kg for 2 - 5 days. The daily dose is divided into four portions, administered SC after dilution to a concentration of 10 mg CaEDTA/ml of a 5% dextrose solution. Clinical improvement can occur in 24 - 48 hours. Do not exceed 5 days of continuous therapy or 2 grams as a single day's total dose because of potential nephrotoxicosis.
    - Psittacine birds - CaEDTA at 35 - 40 mg/kg undiluted IM twice daily for 5 days. Do not exceed 5 days of continuous therapy. Second course of therapy, if needed, is given after a 5 - 7 day waiting period. Seizures controlled with diazepam 0.5 - 1 mg/kg IM BID to TID as needed.
        - See DMSA above.
- Thiamine.
    - Helps symptomatology, best documented in cattle. Given to cattle at 250 - 1000 mg (total dose) BID for 5 days.
    - Does not influence excretion - not a chelation agent.
- Seizure control.
    - Barbiturates (prefer phenobarbital) or diazepam are recommended for seizures when present.

    - Cattle - phenobarbital up to 30 mg/kg IV (to effect) or chloral hydrate 50 - 70 mg/kg IV as a 5 - 7% solution.
- Cerebral edema.
    - Dexamethasone (cattle, horse, 0.1 mg/kg IV, SC, or IM; dog, 1 - 2 mg/kg SC, IM, or IV) and/or mannitol (20% solution, 1 - 2 gm/kg slowly IV) may be indicated for the treatment of cerebral edema, although based on speculation.
- Since lead may be immunosuppressive, broad-spectrum antibiotics may be indicated to control secondary bacterial infections.

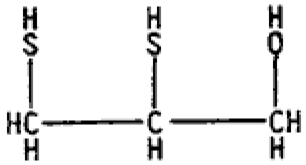
Prevention

- Avoiding exposure is essential.
- Clean up of contaminated soils sometimes can be followed by extraction and recycling of lead.
- Immobilizing lead in soil with $Ca(H_2PO_4)$ is somewhat effective, but this treatment tends to mobilize arsenic in the soil.
- Adding organic material in soil tends to increase its ability to bind metals, including lead. The increase in binding capacity is limited because the organic material will tend to be degraded over time in the environment.
- Altering the pH (alkalinizing) is another method being studied in efforts to immobilize lead in soil.

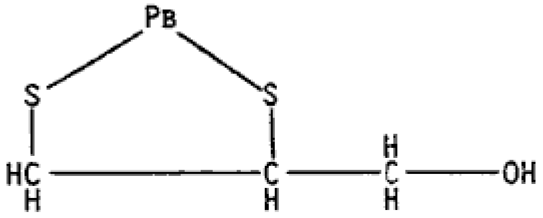
Key Features

- Sources include paint (leaded), used motor oil, storage batteries, lead objects, lead shot, linoleum, etc.
- Mixture of gastrointestinal (colic) effects and CNS (mixed signs), sometimes with effects on red blood cells.
- Rare in cats; almost unheard of in swine.
- Common in dogs and cattle, occasionally encountered in horses.
- Dogs tend to experience the syndrome over several days.
- Cattle may have sudden deaths after a rapid, brief course, or sometimes a prolonged toxicosis.
- Treatment.
    - Sulfate cathartic for precipitation in digestive tract; steps to remove objects.
    - Calcium EDTA, BAL, penicillamine.
    - Thiamine.
    - Control seizures if present.
    - Control secondary infections if present.

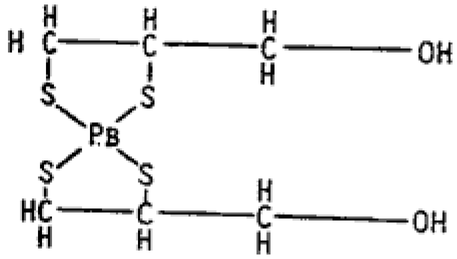
DIMERCAPROL
British Antilewisite (BAL)
(2,3-Dimercapto-1-Propanol)

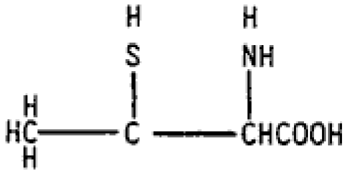


Lead Mono-Bal Complex
(Nonpolar)

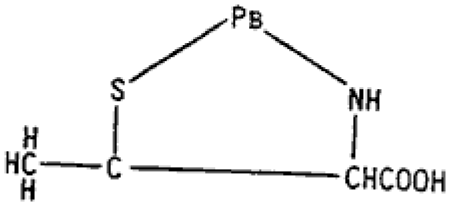


Lead Bis-BAL Complex
(Polar)

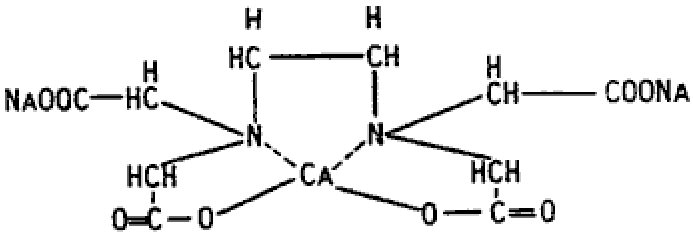




PENECILLAMINE
D-Isomer is the Natural
Form. Penicillamine is the
Most Characteristic Degradation
Product of Penicillin Antibiotics.



LEAD PENICILLAMINE



CALCIUM DISODIUM EDETATE
(Calcium Disodium Versenate) Metal Replaces Calcium

Mercury

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
All species, especially swine, cats	Hours to weeks	Days to permanent damage; poisoning in domestic animals is rare, but poisoned animals often die	

Sources

Mercury is a growing concern in the environment. Mercury may be encountered as:

- Elemental mercury (Hg^o ; in the form of metallic mercury or Hg^ovapor).
- Mercury salts (also called inorganic mercury) such as mercuric chloride, mercuric oxide, etc.

- Organomercurial compounds (includes alkyl forms such as ethyl, methyl, propyl, dimethyl, etc., and aryl forms of mercury, such as phenylmercuric acetate).
- Mercury metal Hg^o .
    - Liquid, volatile (many other mercury compounds are somewhat volatile as well).
    - Mercury circulates in the environment. Because of its volatility the earth continuously "degasses" mercury.
    - Thermometers.
    - Barometers.
    - Dental amalgum used for fillings.
    - Produced from other forms of mercury in aquatic sediments of the environment, but only under anaerobic conditions as sometimes occurs in aquatic sediments. Hg^o is not the major form in sediments.
    - A major source of mercury in the biosphere is mercury vapor produced by burning coal (and to a much lesser extent, other fossil fuels).
    - Metallic mercury is sometimes used in crude gold mining techniques employed in developing countries such as those surrounding the upper tributaries of the Amazon River. This use directly contaminates the local streams and the atmosphere.
- Mercury in manufactured formulations (several compounds; inorganic and organic). As compared to aryl organic mercury compounds, alkyl organics such as methyl or ethyl mercury tend to be more toxic, especially after repeated exposure. Inorganic mercury salts include monovalent mercurous compounds and divalent mercuric compounds.
    - Mildew proof or antifouling paints such as some types used on boat bottoms.
    - Batteries (some small batteries are high in mercury).
    - Fungicides (some are inorganic, many are organic compounds).
    - Fungicide treated seed grains used in feeds.
    - Highly toxic mercurial fungicides have been largely replaced by far less toxic nonmercurial or phenylmercurial fungicides.
- Mercury-containing medications.
    - Mercurial diuretics are similar in toxicity to mercury salts and are no longer used appreciably.
    - Phenylmercuric acetate--sometimes used in dermatology--topical application.
- Sewage sludge may be very high in mercury in some instances.
- Mercury in living organisms.
    - Methyl mercury and, to a lesser extent, ethyl mercury are primary concerns with regard to environmental forms of mercury. All forms of mercury are converted to these by anaerobic bacteria. Methyl mercury is the principle tissue residue form in eggs, regardless of the mercury compound ingested by a bird.
    - Aquatic organisms accumulate methyl mercury from polluted watersheds, bays, etc.
    - Methyl mercury can accumulate in eggs and animal tissues.
    - Dimethyl mercury is also produced in sediments. Like metallic mercury, dimethyl mercury is somewhat volatile and may therefore leave the aquatic ecosystem.

Absorption, Distribution, Metabolism and Excretion (ADME) and Toxicity

- Metallic mercury is fairly low in toxicity when ingested because of fairly low absorption, but poisoning can result if a sufficient amount is ingested (0.01% is absorbed through the GI tract) or when embedded in tissues (be careful not to break thermometers). Laboratory toxicoses are possible from inhalation of much more highly toxic, volatilized metallic mercury. Persons should avoid home-made barometers, etc. Goldminers in South America that burn off metallic mercury used in trapping the gold particles have experienced acute lung and kidney damage.
- Inorganic mercury compounds are absorbed from the lungs, but poorly through the skin and GI tract (7 - 15% absorption); mercury salts can also bind to gut mucosa. Residues in liver, kidney, and plasma (50% is bound to albumin).
- Toxic dose inorganic mercury in horse is 8 - 10 grams. Chronic toxicity can be produced by ingestion of 0.4 mg/kg/day over a several-week period of time.
- Organic mercurials are absorbed via all routes including dermal.
- Alkyl mercury compounds (noncyclic, saturated hydrocarbon compounds) i.e., methyl and ethyl mercury are the most toxic forms of mercury. These compounds initially bind to erythrocytes, become distributed throughout body, and eventually bioaccumulate primarily in brain and to some extent in kidney and muscles. Methyl mercury has a high affinity for the brain and is attached to red blood cells (not much in plasma, therefore, only a small amount is available for hepatic excretion). Methyl mercury is present in eggs when other forms of mercury are ingested.

- Aryl mercurials such as phenyl mercury compounds are slightly less toxic than alkyl mercury compounds on a single dose basis and considerably less prone to bioaccumulate because of catabolism in the liver to free mercury ion with its subsequent excretion via the kidney and large intestine. Aryl mercurials tend to be somewhat less absorbable via the skin, such that some are used in topical medications.
    - Half-life of methyl mercury in cats in one study was reported as = 70 - 74 days.
    - Half-life of mercury in cats was reported in another study as 39 days.
    - Half-life of mercuric compounds is 60 days in man.
    - Half-life of methyl-mercury in humans is estimated at 44 days.
- **Elimination** - Inorganic Hg is eliminated primarily via the urine; organic mercury is eliminated mainly via the bile and feces, less than 10% appears in the urine.
  Note: Marine mammals and some other marine organisms may have extraordinarily high mercury concentrations. This is possible primarily because of formation of insoluble, 1:1 complexes of mercury and selenium intracellularly.

Mechanism

- Sulfhydryl groups of enzymes and other proteins are affected (bound to mercury). Hg readily forms covalent bonds with sulfur. Hg replaces H_2 (Note: 2 atoms) to form mercaptides: X-Hg-SR and $Hg(SR)_2$ (where R = a protein and S = an electronegative radical).
- Associated epithelial and neuron damage may explain some of the problems.
    - Gastrointestinal mucosal damage.
    - Skin lesions.
    - Renal tubular damage (especially with inorganic mercury).
    - Vascular and neuronal damage in the brain (especially with methyl mercury).
    - Blood-brain barrier can be disrupted with less than 1.0 ppm Hg ions in the brain.
- Both methyl mercury and Hg^{++} can disrupt ion exchange across both voltage-gated and ligand-gated channels.
- Mercury may irreversibly inhibit voltage-gated K^+ outcurrent in the early developing nervous system. This may help explain neurologic teratogenicity.
- Methyl mercury-induced neurotoxicity is believed to be the result of an increase in reactive oxygen species caused by a disruption of the mitochondrial electron transport chain. This increase in free radicals in turn depletes glutathione and mediates neuronal injury.
- Methyl mercury also inhibits ATP production and release of Ca^{++} from mitochondria, resulting increased intracellular Ca^{++} concentration, which leads to spontaneous depolarization and release of acetylcholine.
- Methyl mercury decreases uptake of choline by nerve terminals, so there is decreased synthesis of acetylcholine.
- *In vitro*, methyl mercury has been shown to disrupt microtubule assembly and cellular migration.

Signs

- Onset is usually after a period of several days or longer postexposure, although a more acute onset is possible. An acute syndrome can be seen with mercuric compounds due to the corrosive effects on the GI mucosa with resultant fluid and electrolyte loss.
- Neurologic, GI, renal, dermal effects.
- **Cattle**.
    - Stomatitis, salivation, loose teeth, gastroenteritis.
    - Nasal discharge, bronchopneumonia, dyspnea.
    - Dermatitis, pustules, skin ulceration, depilation, hyperkeratinization.
    - Weakness, anorexia, emaciation, prostration, low total protein, low globulin, proteinuria (in severely affected).
    - CNS depression, ataxia, stumbling, hyperesthesia, convulsions (rare).
    - Epistaxis, hematuria, bloody feces, nonregenerative anemia.
    - High fever, severe skin lesions, hemorrhage all give poor prognosis.
- **Swine** - more commonly poisoned with Hg.
    - Anorexia, weight loss, constipation, poor growth.
    - Weakness, flaccid abdominal muscles.
    - Gagging, vomiting.
    - Fever.
    - Thickened, scaly skin.
    - Cyanosis.

    - Blindness.
    - Abnormal posture, staggering, stiffness, disorientation.
    - Depression, tremors, paresis, paddling, coma.
    - Excitation, chewing, but without prehension of food.
    - Death often within 2 - 3 days of onset of major neurologic signs.
    - At high doses: Gastrointestinal upset, tachycardia, CNS depression, cyanosis, hypothermia, dyspnea, coma and death within 1 day.
- **Feline**.
    - Sensitive to environmental mercury (especially methyl mercury in seafood); sentry of environmental/food contamination for humans.
    - Paresis, rear leg rigidity, knuckling over at the carpus and/or tarsus, hypermetria, cerebellar ataxia, tremors, hypersalivation, sensory impairment, tonic-clonic, convulsions.
    - Blindness, persistent vocalizing, paddling, coma, hyperthermia.
    - Weakness, lateral recumbency.
    - Vomiting, diarrhea.
    - Skin pustules.
    - Death.
    - Cerebellar hypoplasia (mimics panleukopenia) and other teratogenic effects in kittens, deaths prior to 3 months of age.
- **Birds**.
    - Reduced hatchability, eggs without shells.
- **General**.
    - Pulmonary damage and associated clinical signs may predominate in cases of inhalation of toxic amounts of Hg^o.

Lesions

- Renal: pale swollen kidneys; renal tubular damage especially affecting the proximal tubular epithelium (P3 segment); glomerulonephritis is possible with chronic exposure due to the antigen-antibody complex deposition.
- Hepatic: liver is pale and reduced in size; microscopic examination may reveal hydropic change.
- Digestive tract: possible necrotic pharyngitis, focal erosive or ulcerative gastritis; necrotic enteritis and typhlitis.
- Brain: no grossly evident brain lesions.
    - Cerebral precapillary arterioles exhibit fibrinoid degeneration especially in swine and cattle.
    - Cerebral laminar necrosis and myelin loss.
    - Cerebral granular layer atrophy and atrophy of calcarine and central cortices in cats; cerebellar hypoplasia and other teratogenic effects, poor survival in kittens.
- Peripheral nerves: myelin and axonal damage.
- Inhalation of mercury vapor may produce an acute, corrosive bronchitis and interstitial pneumonia.

Diagnosis

- Kidney (especially cortex) Hg usually 10 - 15 ppm or more. With time, Hg may decrease to a few ppm. Submit cortex and medulla.
- Much lower concentrations of mercury were associated with severe experimental methyl mercury poisoning in cats.
- Liver and brain are also worth analyzing for mercury (in addition to kidney).
- Gross and histologic lesions (send fixed specimens also).
- Test blood, plasma and urine antemortem, though false negatives are possible in urine as excretion is concentration and time dependent.
- Differential diagnoses: lead, thallium, phenylarsonic feed additive, and ethylene glycol toxicosis, encephalitis, polioencephalomalacia, hog cholera, and erysipelas.

Treatment

- Neurologic damage may be permanent (give appropriate prognosis before owner decides to treat).
- Keep in mind that meat from livestock can be a **hazardous** source of mercury for humans.
- Acute oral exposures:
    - Feed egg then use an emetic if not contraindicated.
    - Activated charcoal and saline cathartic.

    - Sodium thiosulfate orally also safe to bind Hg.
    - Cattle 30 grams orally in a 10% solution.
    - Scarlet Drench Powder, 10% sodium thiosulfate solution.
- Seizures:
    - Diazepam (0.2 - 2.0 mg/kg, IV, to effect) (dogs) or barbiturates (e.g., phenobarbital or, if it fails, pentobarbital) (most species).
    - Fluids and electrolytes for corrosive GI syndrome.
    - Support renal function.
- Any acute mercury toxicosis:
    - **Chelation therapy** in general is not very effective with the organic Hg compounds as only a small fraction is in the plasma and available for excretion.
    - D-penicillamine (15 - 50 mg/kg) orally, but only after gut is free of significant ingested mercury and only if renal function is present, otherwise is dangerous.
    - BAL British Antilewisite (dimercaprol) is not very effective after chronic exposure to organic mercurial compounds. It is contraindicated with organic mercurials as it will increase the brain concentration. BAL also contraindicated with preexistent liver or kidney damage.
        - BAL (in oil) injections may still be recommended for more acutely poisoned small animals (with inorganic mercury sources) although its efficacy is not well documented.
        - BAL - reportedly not highly effective in large animals or humans.
        - Nevertheless, the recommended dose for cattle is 3 mg/kg QID for 3 days, then BID for 10 days; for horses, 3 mg/kg every 4 hours for the first two days, QID on third day, BID for next 10 days (until recovery is complete).
        - When using BAL, it is recommended that one should alkalinize the urine - helps maintain BAL mercury complex which may otherwise dissociate in acid urine and thereby damage renal tubules.
- **DMSA and DMPS**. Mesodimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMSA) are water-soluble analogs of BAL which are less toxic and have greater water solubility than BAL but have limited lipid solubility. They are effective when given orally. DMSA is preferred.
    - **Methyl Hg**. The methyl Hg content of kidney, brain, and liver in mice and guinea pigs was reduced with DMSA (DMPS was less effective in kidney, liver, and it was not effective in brain).
    - DMSA (e.g., Succimer®) was 4 times more effective than N-acetylpenicillamine in increasing urinary excretion of MeHg.
    - In the dog, the most effective method of mobilizing and excreting MeHg was extracorporeal complexing hemodialysis with DMSA. DMSA may confer a sulfur odor to the breath and urine.
    - With inorganic mercurials, DMSA > BAL > DMPS at increasing urinary excretion.

Key Features

- Fungicides, thermometers, barometers, antifouling paints, small batteries, mercury medication and methyl mercury in aquatic organisms from pollution.
- GI, renal, dermal and CNS effects.
- Diagnose by blood and urine Hg antemortem; and renal, brain, liver Hg concentrations and lesions (uncluding histo) postmortem.
- Sodium thiosulfate, D-penicillamine, BAL, or especially DMSA supportive.
- Relay toxicosis to man well documented from consumption of poisoned swine.

Organotin Compounds

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
All species	Hours to weeks	Days to permanent damage; potentially lethal	

Sources

Some wood preservatives, antifouling marine paints, slime-control products used in paper mills, and various antifungal products have contained organotin compounds. Most such products have been withdrawn from the marketplace. Containers of the products may still be available. Also, wetland areas may contain persistent residues.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Topical exposure and ingestion of organotin compounds may lead to toxicosis.
- **Note**: Metallic tin is poorly absorbed and therefore low in toxicity.
- The organotin compounds, trimethyl and triethyl tin, readily penetrate the nervous system.

Mechanism of Actions

- Organotins inhibit oxidative phosphorylation and the Na^+/K^+ pump. Some act by interfering with sulfhydryl groups of mitochondrial enzymes.
- Short-chain trialkyltins (trimethyl and triethyl tins) are neurotoxic:
    - Dialkyltins are hepatotoxic:
        - Cholangitis occurs in species with a common bile duct and pancreatic duct.
        - Tributyl tin can become hepatotoxic after conversion to dibutyl tin.
    - Trialkyl and trialkyl tins (propyl = 3 carbon and longer chain compounds) inhibit T-cell lymphocyte proliferation and thus are immunotoxic.
    - Alkyltins are often mutagens.
    - Larval and, to a lesser extent, older fish are sensitive to triphenyl tin. Developmental defects included.
    - Skeletal malformations. There was also increased mortality.
- Disrupts myelin production in neonates.
- Decreases neurotransmitter concentrations.

Signs and Lesions

- Dialkyl and trialkyltins are potent neurotoxins. Like organomercurials and organolead compounds, a major site of action is the central nervous system.
- Signs may include depression, headaches, loss of libido, irritability, hyperactivity, aggression, weakness, paresis or paralysis.

Diagnosis

- Depends on detection of organotin compounds in source materials, stomach contents, and tissues.
- Initial screening for tin content with atomic absorption spectroscopy or inductively coupled spectroscopy may also be worthwhile.
- Nervous system lesions consistent with organotin poisoning may be noted on histopathologic studies.
- There is no specific treatment for organotin toxicosis. Prevention and limiting absorption are important approaches in preventing harm to animals.

Treatment

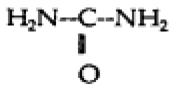
None specific - detoxification and support.

Feed Related Ammonia Poisoning

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Quaternary ammonium disinfectants (ingested)	Dogs	Minutes to hours	Hours; potentially lethal	
Ammonia toxicoses (urea and other sources of nonprotein nitrogen)	Herbivores, especially ruminants	Minutes to hours	Hours; often lethal	

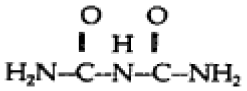
Sources

- Urea, biuret and ammonium salts serve as sources of non-protein nitrogen (NPN) for ruminants. Toxicosis results from the associated build-up of ammonia in the animal.



$H_2N-\underset{\underset{O}{\|}}{C}-NH_2$

UREA



$H_2N-\overset{\overset{O}{\|}}{C}-\overset{H}{N}-\overset{\overset{O}{\|}}{C}-NH_2$

BIURET

- The compounds may be used to furnish up to one-third of the nitrogen protein requirement of ruminant animals.
- The major NPN source in use today is urea, which is commonly incorporated into feed supplements for mixing or blending, range blocks, range cubes, and molasses-NPN combinations.
- Extensively used to supplement cattle feeds, although use has declined in recent years.
- When used as a source of non-protein nitrogen for ruminants, urea is incorporated in rations in amounts not to exceed 1% of the total ration.
- Biuret, when used as a source of non-protein nitrogen, should not exceed 3% of the total ration.
- The improper mixing of the raw chemicals or supplements containing high concentrations of urea, biuret, and diammonium phosphate in feeds prepared for sheep and cattle has resulted in toxicosis and death.
- Ammonium phosphates are used primarily as sources of phosphorus.
- Ammonium salts may be used as expectorants or in the treatment of urolithiasis. The common dose of ammonium chloride as a means of reducing urolithiasis in cattle is 0.75 - 1.5 ounces per cow/day and 0.25 ounces per sheep/day.
- Currently available nonprotein nitrogen (NPN) sources include urea, feed grade biuret, gelatinized starch-urea product, diammonium phosphate, ammonium phosphate solution, ammoniated rice hulls, ammoniated cottonseed meal, ammonium sulfate and mono-ammonium phosphate. Characteristics of representative compounds are shown in the following table:

Content			
Compound	**N %**	**P %**	**Protein Equivalent %**
Urea-pure	46.7	0	292
Urea-feed grade	45.0	0	281
Biuret-pure	40.8	0	255
Biuret-feed grade	37.0	0	320
Monoammonium	12.0	27.0	75
Phosphate	21.0	23.0	131
Diammonium phosphate	21.0	0	131
Ammonium sulfate			

- One part of urea is equivalent to 2.92 parts of protein and 1% protein is equivalent to 0.34% urea.
- To calculate a toxic dose, urea and ammonium salts can be considered together, e.g.:
  - Feed tag states that the feed contains 70% crude protein with 10% from soybean meal and the remaining 60% as protein equivalent from NPN sources. 60% x 0.34 = 20.4% urea content.
  - One kg would contain 204 gm urea enough to poison a 200 - 400 kg animal if rapidly ingested.
- Dry and liquid fertilizers usually contain ammonia, ammonium salts, or urea and may be accidentally ingested.

Toxicity

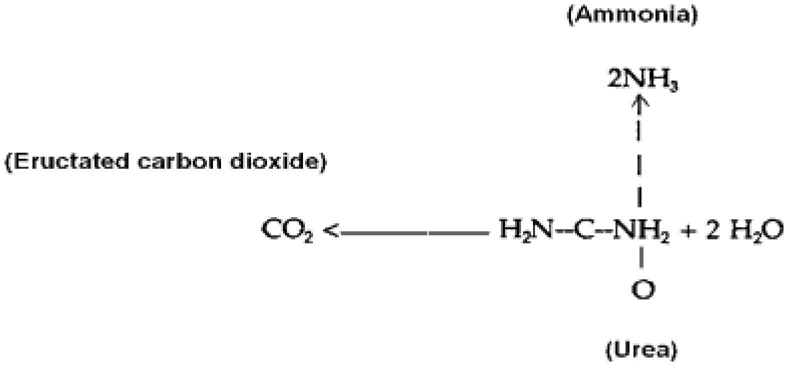
- Most cases of toxicosis are associated with mistakes in mixing, or as a result of feeding supplements containing a high percentage of urea with disregard for the manufacturer's recommendation.
- All mammalian species are susceptible to ammonia poisoning.
- Horses, other monogastrics, and ruminants are all of similar susceptibility to poisoning by **ammonium** salts.
- Ingestion of 1.5 grams/kg of ammonium salts are lethal to monogastric animals.
- The toxicity of the other compounds is dependent on the rates of ammonia formation and absorption. Ruminants are susceptible to poisoning by all compounds used as a source of non-protein nitrogen.
- Because of hydrolysis of urea to ammonia by rumen microorganisms, ruminants are much more susceptible to urea than most monogastrics.
- Ruminants may show signs of mild toxicosis following ingestion of 0.3 - 0.5 grams of urea or ammonium salts/kg body weight. Doses of 0.5 - 1.5 g/kg of urea, urea phosphate, and ammonium salts may be lethal to cattle and sheep.
- Horses are of intermediate susceptibility to poisoning by urea. Doses of 4 grams/kg of urea and 1.4 grams/kg of ammonium salts may cause death in horses.

Predisposing Factors

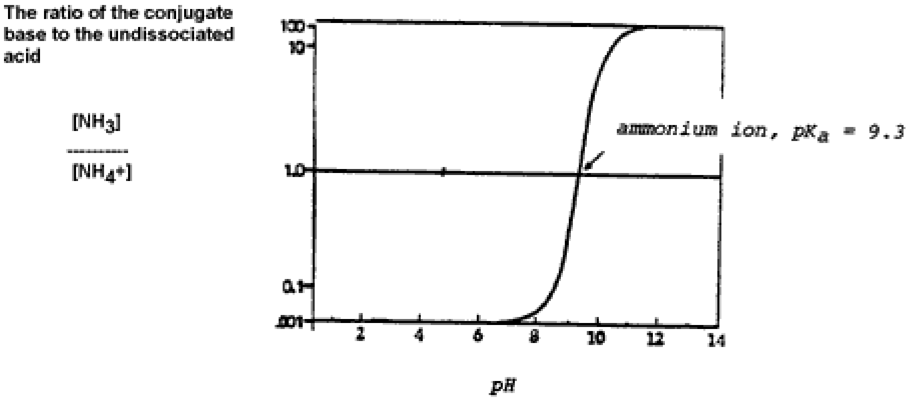
- Several factors including fasting, low energy diets, high rumen pH, elevations of body temperature, dehydration, stress, disease, hepatic insufficiency, lack of natural protein sources, and failure to gradually adapt ruminants to diets containing NPN predispose the animal to urea toxicosis.
- Dietary intake should be carefully monitored during cold weather as the energy needs of the animal rise and cause increased consumption of concentrate mixtures containing NPN.
- Raw soybeans contain urease; but contrary to belief, feeding soybeans does not appear to increase the hazard associated with concurrent exposure to urea.

Mechanism

- The hydrolysis of urea (urealysis) in the rumen is outlined in the following reaction:
  (To portal blood)



- Signs of toxicosis which follow the ingestion of NPN sources or ammonium salts occur as a result of the absorption of ammonia following its release in the digestive tract.
- The rate of release of ammonia from urea depends primarily upon the amount of NPN ingested, the amount of urease present in the rumen, and the pH of the rumen contents. At rumen pHs less than 6.2, the major fraction of the nitrogen released from urea exists as the charged ammonium ion (NH_4+) which is highly water soluble and poorly absorbed. At pH 9.0, NH_3/NH_4+ equals one and large amounts of ammonia are available for absorption.



- Rumen microorganisms have the ability to form amino acids by imitating carbohydrates. To accomplish this, they need a good supply of carbohydrate (a good diet of adequate energy content).
- When rumen flora microorganisms are overwhelmed by excess ammonia produced during urealysis, the ammonia dissolves in rumen fluids, takes on protons to form ammonium ions and thereby increases the pH. As the pH rises (and fewer hydrogen ions are available), the ammonium ions are no longer formed and the concentration of (uncharged) ammonia (NH_3) in rumen fluids and blood increases rapidly. At this time, the clinical signs of ammonia toxicosis become apparent.
- Absorbed ammonia is normally incorporated into the urea cycle and excreted as urea in the urine. The conversion of ammonia to urea (which is more water soluble and excretable) occurs in the liver, and elevation of blood ammonia represents a failure of the liver to convert the excess portal blood ammonia to urea. Hepatic failure produced by ligation of the hepatic artery causes a two- to three-fold increase in the ammonia concentrations in muscle, brain and pancreas.
- Ammonia inhibits the Kreb's cycle and there is a compensatory increase in anaerobic glycolysis with resultant lactic-acidemia.
- High brain ammonia concentration interferes with cerebral energy metabolism and the sodium-potassium-ATPase pump.
- Hyperkalemia has been associated with lethal effects on the heart.

Signs

- Within 10 minutes to 4 hours following the ingestion of excess urea or other NPN sources, animals may exhibit frothy salivation, depression, hyperirritability, grinding of teeth, abdominal pain, increased defecation, and polyuria.
- Muscle tremors, incoordination, increased respiratory rate, and general weakness are commonly noted. Animals may appear blind.
- Bloat and regurgitation of rumen contents may occur, especially in sheep. Recumbency, hyperthermia, anuria, cyanosis, and convulsions are common terminal signs.
- The clinical course of the toxicosis is usually from 0.5 - 4 hours.
- Signs appear when rumen ammonia and blood ammonia concentrations exceed 80 mg/100 ml and 2 mg/100 ml, respectively.
- Hyperkalemia has been associated with lethal effects.

Lesions

- Postmortem examination may reveal few changes, but an odor of ammonia is often noted in rumen contents and tissues.
- Although there are no definitive lesions, pulmonary edema, petechial hemorrhages, and generalized congestion are common findings.
- Animals bloat rapidly, and carcasses seem to decompose more rapidly than normal.

Diagnosis

- Clinical signs and a history of acute illness following ingestion of urea or other NPN sources are important in establishing a presumptive diagnosis.

- Chemical analysis of suspect feeds, rumen fluid, and jugular whole blood or serum are requisite for a definitive diagnosis. Blood ammonia values ranging from 1 - 4 mg/100 ml and rumen ammonia values greater than 80 mg/100 ml are compatible with a diagnosis of ammonia toxicosis. Samples of blood and urine should be collected immediately after death and specimens should be frozen if tests cannot be done in 1 hour. Composite samples of rumen fluids should be obtained. When blood and rumen contents are not preserved properly, autolysis and proteolysis of rumen contents may raise NH_3 concentrations 20 -50 mg/dl above those that existed at death, which may give false positive interpretations.
- The excess NPN is often found in the feed.
- Significant increases in the packed cell volume, blood ammonia, blood glucose, blood urea nitrogen, serum potassium and phosphorus, rumen pH, rumen ammonia and SGPT are noted during ammonia toxicoses. Blood pH and urine production are decreased.

Differential Diagnosis

- Several conditions including toxicosis from organochlorine or organophosphorus insecticides and cyanide, as well as protein or grain engorgement, enterotoxemia, meningitis, and encephalitis should be considered as possible alternatives to ammonia intoxication.
- Rumen pH values existing in various disorders serve as an aid in establishing a diagnosis.

Rumen pH Values (Lloyd, 1973)

Condition	Rumen pH
Urea poisoning	8.0 - 9.2
Protein engorgement	7.5 - 8.5
Fasting	6.8 - 7.3
High grain diet	5.5 - 6.2
Mild grain indigestion	4.5 - 5.5
Acute grain overload	3.4 - 4.5

- A rumen pH of 4.0 - 7.6 is required for proper rumen motility.

Treatment

- Effective only if initiated early in the course of the toxicosis. Most effective when given within 20 - 30 minutes after the appearance of clinical signs.
- Recumbent animals almost never respond.
- The best treatment for cattle consists of administration of a combination of 5 - 10 gallons of cold water and a gallon of 5% acetic acid (or vinegar) by means of a stomach tube. The cold water reduces the temperature of the rumen and thus the rate of urease action. The acetic acid reduces the rumen pH and converts the readily absorbed ammonia present in ruminal fluids to the relative innocuous ammonium ion. The drop in rumen pH also slows urease activity. When performed on nonrecumbent animals showing tetany, recovery with return of normal rumen pH and fermentation occurs within 48 hours. Retreatment may be needed depending upon the response of the animals.
- Intravenous fluids should be administered to insure adequate urine flow.
- When bloat occurs, it should be relieved immediately.
- Some people suggest that rumen lavage via a rumenotomy incision or trochar may be superior to cold water/acetic acid.

Key Features

- Ingestion of a NPN source in excessive amounts or by unaccustomed animals or by animals on a low-energy ration.
- Ruminants most susceptible to urea; horses intermediate; all species affected by ammonia salts.
- NH_4^+ innocuous but NH_3 from urea builds up causing most toxic effects.

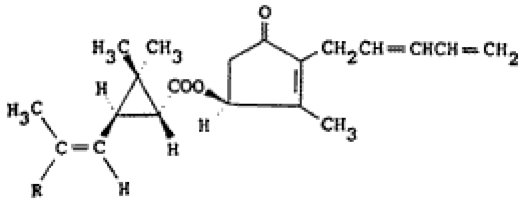
- Rapid syndrome, polyuria, bloat, abdominal pain, tremors, incoordination.
- Diagnosis: Very high rumen pH, determine rumen and blood ammonia concentrations + analyze feed.
- Therapy comprised of relieving bloat, cold water and vinegar, fluids, control of severe neurologic signs enough to treat.

Pyrethrum (Pyrethrins) and Pyrethroids

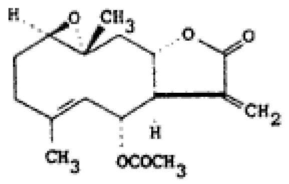
Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Cats, dogs	Minutes to hours	Hours (usually) to two days; rarely lethal	

Sources

- Pyrethrins are natural insecticides produced by certain exotic *Chrysanthemums* (sometimes called *Pyrethrum*) flowers, not by domestic horticultural varieties. Pyrethrum contains pyrethrins and cinerins.
- Pyrethroids are synthetic insecticides.
- Used in numerous formulations including aerosols, sprays, dusts, tags, dips, and shampoos. Some formulations include additional insecticides and/or insect repellants. Flea control products constitute the primary source of exposure leading to problems in small animals.



Pyrethrin I
R = CH_3
Pyrethrin II
R = $COOCH_3$



Pythrethrosin

Toxicity

- Toxicity varies with the specific compound and route of administration involved.
- In general, introduction of an alpha cyano moiety (type II pyrethroids) results in an increase in toxicity.

Rat LD_{50} (mg/kg)		
Type I Compounds	**Oral**	**IV**
Pyrethrin I	900	
Allethrin	680	
Tetramethrin (phthalthrin)	4,640	
Kadethrin	600	
Resmethrin	100	7
Phenothrin	10,000	> 300
Permethrin	2,000	>135
Cismethrin		5
Bromophenothrin		>30
Rat LD_{50} (mg/kg)		
Type II Compounds	**Oral**	**IV**
Fenpropathrin	25	1

Cypermethrin	500	6-9
Deltamethrin (decamethrin)	31	2
Fenvalerate	450	20
Fluorocyphenothrin		5-7
Fluvalinate	1,000	
Dowco 417	460	
Flucythrinate	67	
Bay-FCR	590	

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rapid hydrolysis of ester linkage in digestive tract results in low oral toxicity.
- Most are rapidly metabolized by ester hydrolysis and via oxidation by liver microsomal enzymes.
- The resulting alcohol, phenol, or carboxylic acid metabolites are often conjugated with glycine, glucuronide, sulfate, and glucoside prior to excretion.
- Residues: follow label recommendations on withdrawal, usually not a problem.

Mechanism

- Pyrethrins and type I pyrethroids act on sodium ion channels; decreasing peak sodium conductance, prolonging the sodium conductance, and suppressing potassium conduction. These changes result in decreases in the amplitudes of action potentials and repetitive nerve discharges. Nerve conduction block can occur.
- Type II pyrethroids (contain a cyano group) also act on sodium ion channels which is thought to account for the sensory nerve stimulation associated with paresthesias in humans (and presumably other species). A depolarization of nerve membranes without repetitive discharges occurs with decreased action potential amplitudes.
- Type II pyrethroids are also believed to interfere with the binding of GABA and glutamic acid at their respective nervous system's receptor sites.
- Allethrin (and perhaps other pyrethroids) allosterically affects binding at the acetylcholine nicotinic receptor.
- Pyrethrins and pyrethroids also inhibit various adenosine triphosphatases including the calcium-ATPase and the calcium magnesium-ATPase in nervous tissues.
- Increased cerebellar concentrations of cyclic GMP (but not cyclic AMP) occur before the development of seizures in cypermethrin (and perhaps other pyrethroid)-poisoned rats. With *in vitro* exposure to cypermethrin, however, the cGMP concentration was unaltered. It is therefore believed that the increase in cGMP concentration is a secondary, rather than a primary, effect. Increased cerebellar cyclic GMP is sometimes seen with other agents causing seizures.
- Synergists-Addition of mixed function oxidase inhibitors, such as piperonyl butoxide, N-octyl bicycloheptene dicarboxiimide MGK264, sesame oil (and/or several others) enhances toxicity in insects and mammals by prolonging the life of the intact, active form of the insecticide in the body.
- In most cases at this time, the actual cause of clinical signs is unknown: possibly insecticide, synergist, or solvent. This is due to a lack of adequate toxicity testing.

Susceptible Species

- Small animal poisoning occurs principally in **cats**.
- Rodents.
- Fish are often extremely sensitive.

Signs

- Often associated with vigorous insecticide treatment of the animal.
- Possibly due in part to larger amounts of synergist(s) in the formulation.
- Effects on rodents classified into two syndromes: type I and type II syndromes which correlate with the chemical structures.
    - Type I syndrome: classical pyrethrins and type I pyrethroids (no alpha cyano group).
        - Increased sensitivity to stimuli, fine muscle tremors, whole body tremors, prostration.

  - Type II syndrome-alpha-cyano pyrethroids.
    - Salivation; rodents paw, burrow, writhe, and may display clonic seizures; possible paresthesia of skin.
- In cats and dogs, clinical signs associated with toxicosis from pyrethrins and type I or type II pyrethroids may include tremors, increased salivation, ataxia, vomiting, depression, increased body temperature, hyperexcitability or hyperactivity, seizures, dyspnea, and death.
- Clinical signs generally develop within hours of exposure, but may be delayed as a result of prolonged exposure from dermal absorption or grooming.
- Generally, sublethally exposed animals recover within 72 hours.

Lesions

- No specific gross lesions noted.
- Deaths generally rare.

Diagnosis

- Based upon a history of a potentially toxic level of exposure to a pyrethrin or pyrethroid containing insecticide and the development of compatible signs.
- Rule out other insecticides, e.g., organophosphorus and/or carbamate compounds, in part by measuring acetylcholinesterase activity.
- Chemical analysis of pyrethrin/pyrethroid residues on skin of animal will confirm exposure. Tissue concentrations of pyrethrins/pyrethroids may support a tentative diagnosis of poisoning but diagnostically confirmatory concentrations in tissue are not yet established.

Treatment

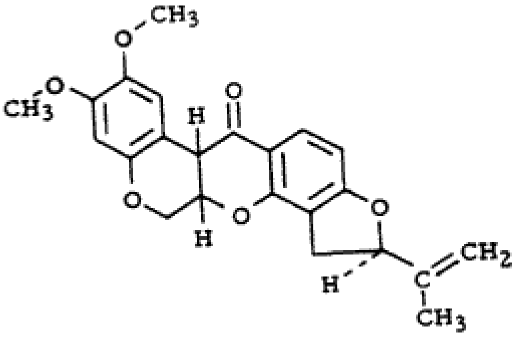
- Topical exposure: bathe thoroughly with detergent.
- Recent oral exposure (within a few hours): (Early) emetics if not contraindicated; activated charcoal and saline cathartic.
- For severe CNS stimulation with seizures:
  - To treat pyrethroid toxicosis in dogs, try diazepam (0.2 - 2.0 mg/kg IV to effect). If this fails, parenteral phenobarbital is recommended. If it too fails, induction of anesthesia with pentobarbital may be necessary.
  -
- Cats with severe tremors due to inappropriate use of concentrated permethrin often improve after IV administration of methocarbamol (Robaxin Vâ) at 55 - 220 mg/kg. Half the dose should be given rapidly but no faster than 2 ml/min. Administration should be discontinued briefly as the cat relaxes, then resumed until the desired effect is achieved. The maximum dose on the label (330 mg/kg) should not be exceeded. Initial treatment with diazepam or pentobarbital, or mask induction with isoflurane may be needed for control of seizures.
- Atropine can reduce some clinical signs (e.g., diarrhea, hypersalivation). However, in experimental studies with lethally poisoned laboratory animals, atropine minimized excessive salivation and diarrhea without affecting the observed LD$_{50}$.
- Muscle relaxants, e.g., methocarbamol at 55 - 220 mg/kg IV at a rate not to exceed 200 mg/minute, may be of benefit.
- Phenothiazine tranquilizers are contraindicated.
- Symptomatic and supportive therapy.

Rotenone

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Cats, dogs, birds, fish, amphibians	Minutes to hours	Hours to days; infrequently lethal except in aquatic organisms and arthropods	

Sources

- Derived from roots of the *Derris* and *Lonchocupus* plant.
- Synonyms derrin, nicourine, and tubatoxin. (All these terms are rarely used.)
- Used historically in Malaya and South America to kill fish and for poison arrows.
- Insecticide.
- More toxic than pyrethrins.
- Formulated into products for use in gardens and on dogs and cats (dips, sprays, powders). Formulations include dusts of 0.75 - 1.5% concentration, emulsifiable concentrates, wettable powders of 5% concentration, solutions (up to 57%) and resins.
- Products may be synergized with piperonyl butoxide.



Rotenone

Toxicity

- Highly toxic to birds and fish, may affect any species.
- Cats most often affected after deliberate use of rotenone containing products for ectoparasitism.
- Oral LD_{50}s **in laboratory animals range from 10 to 30 mg/kg.**
- LD_{50} **IP (mice) = 2.8 mg/kg.**

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rotenone is metabolized by liver, undergoes hydroxylation to form equally toxic rotenoids. Detoxification in liver by demethylation can also occur.

Mechanism

- Rotenone blocks NAD-flavin electron transport in respiratory metabolism which results in blockade of nerve conduction. Specifically, interferes with the electron transport process between flavoprotein and ubiquinone (coenzyme Q). Also blocks oxidation of NADH.

Signs

- Pharmacologic effect-anesthetic effect when in contact with nerve axon or mucous membrane.
- Oral exposure:
    - Gastric irritation.
    - Vomiting.
    - Poor absorption.
- Dermal exposure:
    - May cause problems in dogs; more often in cats.
    - Possible skin irritation and severe pulmonary irritation from inhalation of dust.
    - Signs may include vomiting, lethargy, tremors, stupor, clonic, repeated convulsions, respiratory failure, dyspnea and death.
    - Possible hypoglycemia.
    - Death occurred in a 6-month-old Persian cat apparently as a result of being dipped in a rotenone dip. **Note**: Long-haired cats may dermally absorb much more of any type of insecticide due to prolonged contact with the wet insecticide (whether prolonged volatilization

and inhalation of vapors of some such compounds also contributes to systemic absorption is not certain but seems plausible).

Pathology

- Pulmonary congestion, gastrointestinal tract irritation.
- When chronically fed to rats or dogs, passive congestion of the liver with midzonal necrosis was observed.

Treatment

- Oral exposure: avoid fatty or oily foods as they enhance absorption.
- Minimize fraction absorbed: depending upon route of exposure and condition of patient (bathe with detergent, emetic, enterogastric lavage, activated charcoal, saline cathartic).
- Monitor blood glucose, administer glucose as needed. May not enhance survivability.
- Monitor acid-based status and, if necessary, correct metabolic acidosis with diluted bicarbonate (slow iv).
- Vitamin K3 (do not use in the horse) which activates a bypass of the rotenone sensitive site has been recommended based on theoretical (*in vitro*) rather than experimental *(in vivo*) grounds.
- If a solvent vehicle has been used, it may be necessary to manage as a petroleum hydrocarbon ingestion (see pulmonary toxicants).
- Supportive and symptomatic care.

Tricyclic Antidepressants

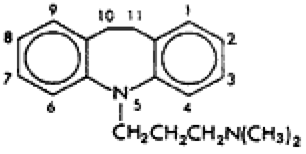
Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Dogs, cats	Minutes to hours	Days; often lethal	

Chemical Structure

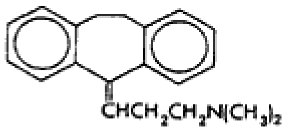
- Term tricyclic is derived from the 3-ring chemical structure of the central portion of the molecule.
- Tertiary amines exist within the tricyclic class.
- Amoxapin has a 4-ring structure but is classified as a tricyclic antidepressant (TCA) since it retains the classic 3-ring moiety.

Tricyclic Antidepressants and Trazodone

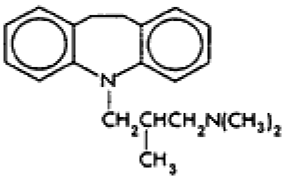
Tertiary Amines



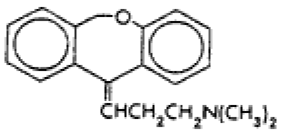
Imipramine



Amitriptyline

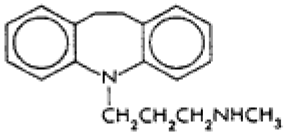


Trimipromine

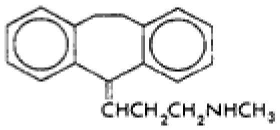


Doxepin

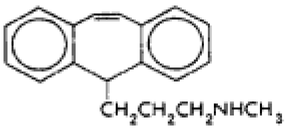
Secondary Amines



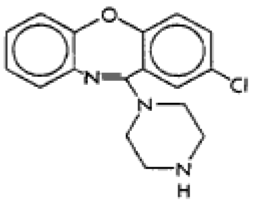
Desipramine



Nortriptyline

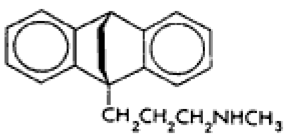


Protriptyline

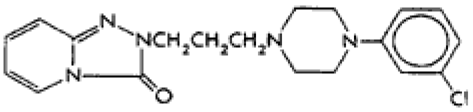


Amoxapine

Atypical Antidepressant



Maprotiline



Trazodone

Sources

- Increasing use as antidepressants in human medicine.
- Represent most common life-threatening drug ingestion in human patients.
- Infrequently encountered in veterinary medicine, however accidental poisoning incidence is on the increase.

Toxicity

- In general, 15 - 20 mg/kg is thought to be potentially lethal in human patients.

Absorption, Distribution, Metabolism and Excretion (ADME)

- TCAs in therapeutic (human) doses are rapidly absorbed from the GI tract. Have high lipid solubility. Large ingestions may result in prolonged GI absorption due to anticholinergic effects and associated decrease in GI motility.
- Highly protein bound.
- Free TCA concentration can be decreased by alkalinization of serum.
- Primarily undergo liver metabolism: demethylation or hydroxylation followed by glucuronidation. Note this may be an important consideration in cats.
- Variable elimination half-lives from 10 - 81 hours.

Mechanism of Action

- Inhibition of biogenic amine (serotonin, norepinephrine) uptake centrally. Regulate it higher availability causes generalized CWS stimulation.
- H_1 and H_2 histamine receptor antagonists.
- Quinidine-like cardiac effects are the most life-threatening effects of TCA overdose (4).

Clinical Signs

- Humans.

  - Generally develop within hours of ingestion.
  - Primarily involve CNS, parasympathetic nervous system, and cardiovascular systems.
  - Tachycardia, CNS excitation (early), convulsions, coma, hypotension, arrhythmias, and cardiac arrest.
  - EKG alterations include prolonged QRS intervals which correlate with arrhythmias and seizure development. PR and QT prolongation. Sinus tachycardia common; but various arrhythmias possible.
- Dog.
  - Vomiting. Behavioral changes including disorientation, "anxiety®, and aggression have been reported. Severe depression to semicomatose status. Seizures have been observed.
  - Cardiac abnormalities include tachycardia, bradycardia, and arrhythmias.
  - Hypothermia, ataxia, weakness, tremors, and shock also occur.
  - Experimental studies in dog with amitryptyline resulted in increased heart rate and prolonged QRS duration. Ventricular tachyarrhythmias occurred in almost all dogs.
  - Progression of signs can be very rapid. Death may occur within 1 - 2 hours of ingestion if left untreated (4).

Treatment

- Due to general lack of information in the veterinary literature, the following treatment recommendations are based on current management of human patients.
- Maintain airway, support respiration.
- Gastric lavage with administration of activated charcoal and cathartic.
- Consider emetic **only** in recent exposure and only if animal is still alert. Generally, emesis is **not** recommended since seizures may occur abruptly.
- Repeated oral doses of activated charcoal every 2 - 3 hours may enhance elimination.
- Seizure control-try diazepam (Valium) first. Long-acting anticonvulsants (phenobarbital) should be administered concurrently. Valium has been effective in poisoned dogs.
- Seizures can produce metabolic acidosis which enhances cardiotoxicity, therefore sodium bicarbonate (administered at 1 - 3 mEq/kg) is **strongly** indicated. Experimentally shown efficacious in poisoned dogs. Best to monitor acid base status.
- Phenytoin has been used with variable success in treating seizures and cardiac arrhythmias in human patients.
- Ventricular arrhythmias can also be managed with lidocaine in the dog. Quinidine sulfate, procainamide, and disopyramide are contraindicated in TCA poisonings.
- β blockers, e.g., propranolol, have had variable success in treating TCA cardiotoxicity. May be of some benefit in sinus tachycardias. However, β_1 selective blockers such as metoprolol or esmolol may be preferred to avoid inadvertently causing bronchoconstriction.
- Hypotension should be corrected with fluid therapy.
- Symptomatic therapy.
- TCA management requires close patient monitoring for a minimum of 6 - 12 hours postingestion.

Fumonisins

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Horses, and possibly rabbits may have neurologic effects	Several days to months	Permanent damage likely in horses that survive; often lethal	

Sources

- Fumonisins are mycotoxins produced by the fungus *Fusarium moniliforme* primarily in corn. Fumonisin B_1 is generally the dominant toxin present.
- Worldwide distribution, primarily associated with feeding of corn or corn products.
- Corn screenings, taco plant sweepings, or whole shelled corn is often involved. The infested corn may appear grossly normal.

- The presence of *F. moniliforme* in corn is not diagnostic since nearly all corn in the USA is contaminated by this organism.
- Several climatic factors predispose to fungal growth and toxin production such as: midsummer drought, an early wet fall, fluctuating warm and cold temperatures, accompanied by an early frost and delayed harvests.
  - During a drought year (1989), fumonisin B_1 was detected in Illinois corn at over 250 ppm.
  - In 1995, corn in Texas was found to contain fumonisin B_1 at up to 100 ppm.

Susceptible Species

- Horses, ponies, and donkeys may develop leukoencephalomalacia and/or liver failure.
- Other species such as swine and rabbits may be poisoned by fumonisin-contaminated corn although the syndrome is different.
  - Swine develop pulmonary edema.
  - Rabbits may develop renal failure.

Mechanisms of Action

- Fumonisin B_1 apparently causes its toxic effects, at least in part, by inhibiting the action of sphingosine N-acyltransferase, an enzyme involved in the conversion of sphinganine and sphingosine into sphingolipids.
- Sphingosine is an important second messenger in a range of cell types.
- Sphinganine can be very cytotoxic or can lead to cell proliferation and affect a wide variety of cellular systems. Inhibition of N-acyltransferase may cause increases in sphinganine concentration in tissues.
- Sphingolipids are important in regulation of cell growth, differentiation, and neoplastic transformation. Alteration in sphingolipid concentrations and functions, especially in the vasculature, also are believed to contribute to the major signs and lesions of fumonisin toxicosis.
- In horses with leukoencephalomalacia, regional brain tissue sphingolipid alterations were not evident which may suggest that the primary site of fumonisin action causing the "stroke-like" lesions may be the endothelial cells of the vasculature.
- Swine develop severe pulmonary edema in fumonisin toxicosis. It is theorized that, in this species, fumonisin causes damage to hepatocyte membranes causing release of membrane fragments to the circulation. These are trapped in the lung where they are engulfed by pulmonary intravascular macrophages which may release substances that activate neutrophils and alter capillary permeability resulting in pulmonary edema.
- Cardiac failure and pulmonary hypertension, due to pulmonary vasoconstriction, also may occur in swine, predisposing them to pulmonary edema.

Signs in Horses

- Poisoning in the USA most often occurs in late fall or early winter.
- Onset may occur as early as 7 days after a new batch of corn is first fed, but first signs are usually seen after 14 - 21 days; occasionally onset may be delayed 90 days or more.
- Outbreaks on the same farm affecting several horses are common; sometimes other local herds are also affected. Horses in various stages of the disease will often be present.
- In 1901 - 02, over 2,000 horses reportedly died in the USA as a result of leukoencephalomalacia; and in 1934 - 35, over 5,000 horses died as a result of this syndrome in Illinois alone.
- In a given outbreak, the overall morbidity is generally low, less than 25%; but mortality usually approaches 100% in affected animals.
- **Neurotoxic syndrome**: the clinical course is generally short with an acute onset of signs and deaths within 2 - 3 days. This syndrome is currently termed equine leukoencephalomalacia (ELEM), although historical names include blind staggers, cerebritis, leukoencephalitis, encephalomyelitis, cornstalk disease, moldy corn poisoning, foraging disease, and cerebrospinal meningitis.
  - The neurotoxic form progresses over hours (usually) to 4 - 5 days. Surviving horses may be encountered on occasion, and some such animals have permanent neurologic deficits.
  - T,P,R are all normal, at least initially.
  - Partial anorexia often occurs early in the course.
  - Depression, ataxia, blindness, and hysteria are common.
  - Head is often held low, especially when left alone.
  - Reluctance to move and loss of equilibrium are noted in some horses when forced to walk.

    - Anorexia progresses and coincides with glossopharyngeal paralysis, paralysis of the lips and tongue, and loss of the ability to grasp and chew food.
    - Incoordination increases.
    - Aimless walking, circling, and ataxia often occur.
    - Head pressing, marked stupor, and hyperesthesia are common.
    - Hyperexcitability, profuse sweating, delirium, mania, or convulsions are often present, especially terminally.
    - Blindness is usually unilateral and often "progressive" when it occurs.
    - Lateral recumbency often occurs, most often within 4 - 12 hours of onset.
    - Convulsions.
    - Acutely affected animals often progress through the manic and depressive stages of the syndrome within 4 - 12 hours of the onset and become recumbent and moribund.
    - Death-may occur without previous signs being noted.
- **Hepatotoxic syndrome**:
    - With the hepatotoxic form, there are usually 5 - 10 days between the onset and death.
    - Icterus is usually prominent in horses with hepatic degeneration. There may also be edema of the face and submandibular space and oral petechia. Elevated bilirubin, liver enzymes are typically present.
    - Terminal diaphoresis, coma, and sometimes clonic convulsions may be noted, presumably due to hepatoencephalopathy.

Signs in Swine

- Decline in feed consumption is usually the first sign. If toxin consumption is significant, acute pulmonary edema and, often, death follows. Onset of pulmonary edema may be delayed for up to 7 days after feeding of fumonisin-contaminated feed is begun and typically deaths cease within 48 hours after withdrawal from contaminated feed.
- At low doses, slowly progressive liver disease may occur.

Signs in Other Species

- Poultry-poor performance, feed refusal, diarrhea, weakness, and high mortality may be noted.
- Rats-hepatic neoplasia.
- Rabbits-sudden renal failure.
- Human beings-esophageal cancer is suspected to be related to consumption of fumonisin-contaminated corn.

Lesions: General

- In all mammals studied to date hepatic lesions have been found.
- Effects on other organs vary among species (species-specific effects).

Lesions in Horses

- There are two syndromes in the horse that may appear independently or concurrently:
    1. The classical nervous form with liquefactive necrosis in the white matter (may occur as a result of low consumption over a long time).
    2. A primary hepatocellular disease with secondary hepatoencephalopathy (may occur due to consumption of large amount of affected corn over a short time).
    - **Lesions of both types may be present**within the same animal or within the group.
- The liquefactive necrosis in the subcortical white matter is usually evident grossly; the surface of the brain may look normal, but the liquefaction may extend into or even through the cortex in some horses.
- The cavities are fluid-filled and there may be variable degrees of hemorrhage. Adjacent to these areas, the brain may have a greenish-yellow, granular appearance.
- Mild cases may exhibit only histologic lesions, consisting of a perivascular reaction, with infiltration of mononuclear and plasma cells and occasionally eosinophils; there may also be astrocytosis.
- The liver may be small and firm.
- Liver lobules tend to have a red center and a yellow periphery, resulting in an increased lobular pattern.
- Histopathologic examination of the liver may reveal centrilobular necrosis, and moderate to marked periportal fibrosis.

- Gross lesions occasionally reported that involve other organs include congestion of the lungs, intestinal mucosa, and kidneys, as well as petechial hemorrhages on the epicardium.

Lesions in Swine

- Severe pulmonary edema and hydrothorax.
- Congestion of alveolar septa without hyperplasia or fibroplasia.
- Focal to massive pancreatic necrosis is sometimes noted with dissociation and rounding of acinar cells.
- Hepatocellular cytomegaly, disorganized hepatic cords, and early perilobular fibrosis have been reported.

Lesions in Other Species

- Rats-hepatic neoplasia, renal tubular nephrosis.
- Rabbits-acute proximal tubular necrosis.
- Broilers-multifocal hepatic necrosis, thinning of the thymic cortex.

Diagnosis

- History of ingestion of corn in diet.
- Culture for *F. moniliforme* can be somewhat supportive but is not diagnostic.
- Clinical signs and lesions.
- Characteristic liquefactive necrosis of white matter in the brain may be only histologically evident even in lethally affected horses.
- Detection of approximately 10 ppm fumonisin in horse feed or 50 ppm in swine feed.
    - Assays are now available at most veterinary diagnostic laboratories.
    - An ELISA-based screening test for fumonisin is sold by Neogen.

Treatment

- Isolate affected horses to prevent other horses from traumatizing them or vice versa.
- Be careful: horses may be dangerous (crazed).
- Thiamine may help-but is not a panacea. There are no data demonstrating a benefit from thiamine treatment.
- Activated charcoal at one pound per head and a saline cathartic for the first two days could be tried. There are no studies to illustrate whether or not it would be of any benefit. Most damage may have already occurred but if not tried, no benefit could be realized.
- Change of diet-avoid corn.
- Support, quiet surroundings, maintain hydration, etc.

Prevention

- For equine species, it has been recommended that the non-roughage portion of the diet contain less than 5 ppm fumonisin B_1. This is a **narrow** margin of safety.
- For swine, it has been recommended that the total diet contain less than 10 ppm fumonisin B_1. This is a **narrow** margin of safety
- For dairy cattle, no level has been recommended.
- For beef cattle, it has been recommended that the non-roughage portion of the diet contain no more than 50 ppm fumonisin B_1.
- For poultry, it has been recommended that the total diet contain less than 50 ppm fumonisin B_1.

Key Features

- *F. moniliforme* contaminated corn (almost always).
- Equids, outbreaks usually affect several horses over a period of days.
- Neurotoxic form-rapid death after sudden onset of bizarre neurologic deficits and behavioral effects.
- Hepatotoxic effect-more gradual: hepatoencephalopathy may result.
- Neurologic form: liquefactive necrosis, perivascular reaction on histopathologic examination.
- Liver may be small, firm, with an increased lobular pattern.
- Most horses die; those surviving usually have neurologic (brain) damage.

- Severe pulmonary edema with marked hydrothorax in swine.
- No known effective therapy.

Centauria - Yellow Star Thistle and Russian Napweed Cause of "Chewing Disease" of Horses

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants with Mixed Effects on the Central Nervous System
Horses	Days to months	Permanent damage often lethal	

Description

- Yellow Star Thistle (*Centauria solstitialis*).
    - Annual weed, branches from the base to about 1 foot in height.
    - Leaves densely covered with cottony hair.
    - Flowers-composite heads, terminal with ovoid spiny base and terminal spreading cluster of bright yellow florets, early stage looks like dandelion.
- Russian Napweed (*Centauria repens*).

Habitat

- Yellow Star Thistle.
    - Primarily western, especially the dry pastures of northern California, also spreading in northwestern states; rare if at all in South and East. Extremely costly to eliminate with herbicides.
- Russian Napweed (*Centauria repens*).
    - Western 1/2 of USA.

Toxic Principle - Unidentified

Dried plants are reportedly still toxic as cases of apparent toxicosis have occurred as a result of consuming hay containing the plant.

Toxicity

Some horses have grazed at least 110 days with no problem; others exhibit onset by 30 days, most from 30 - 90 days of grazing. Signs begin after consumption of several hundred pounds of these weeds.

Mechanism

- Signs are reportedly a result of hyperirritability of the CNS and loss of control (loss of neuronal connections) from the higher centers. The initial signs are believed to result from release of dopamine from nigrostriatal nerve endings and the later signs may be due to dopamine deficiency. Impairment of drinking and eating may be due to damage to neural areas supporting cranial nerves V, VII, and XII.
- Focal reflexes and sensations reportedly remain intact.

Usual Signs

- Hypertonicity of facial and lip muscles, upper lips are pulled over teeth, lower lip hangs, may traumatize lips.
- Tongue lolling.
- Horses perform chewing movements but are unable to obtain food or to swallow it.
- Mouth may be held open with the tongue protruding. However, the animal is able to withdraw the tongue and there is not a flaccid paralysis.
- Yawning.

- Head tossing.
- Chews food; then food drops out of mouth; food never gets to pharynx.
- May eventually "lose interest" in food.
- Also can't drink normally, may immerse head into water to the level of the pharynx so it can be swallowed.
- Sometimes signs are unilateral, but then progress.
- Death occurs as a result of starvation in most horses.
- Prognosis is uniformly poor.

Rare Signs

- Abnormal gait, incoordination, hypermetria, tremors, extreme depression.
- Dyspnea, inhalation of food, secondary gangrenous pneumonia.

Lesions

Nigropallidoencephalomalacia: areas of ischemic necrosis and malacia with gitter cells clearing necrotic debris in the substantia nigra, which is just posterior to the pituitary, and/or in the globus pallidus, which is at the base of the brain, in front of the optic chiasma. Most lesions are bilaterally symmetrical.

Thiaminase-Containing Plants and Other Substances

V. Beasley

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Pteridium Aquilinum (Also Called *Pteris Aquilina*) - Bracken Fern

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Thiaminase-Containing Plants and Other Substances
Horses	Weeks to months	Weeks to permanent damage; potentially lethal	

Synonyms - Brake fern, hog brake

Description

- Native perennial herb, which spreads by means of a deep, stout, especially toxic horizontal rhizome. The rhizome is often below plow depth and results in growth of large patches of the plant.
- Triangular coarse, leaves (fronds) tend to be erect. Fronds are palatable.
- Up to 6 feet tall.
- Spores in late summer; sporangia are protected by the rolled under edges of the blades.

Habitat

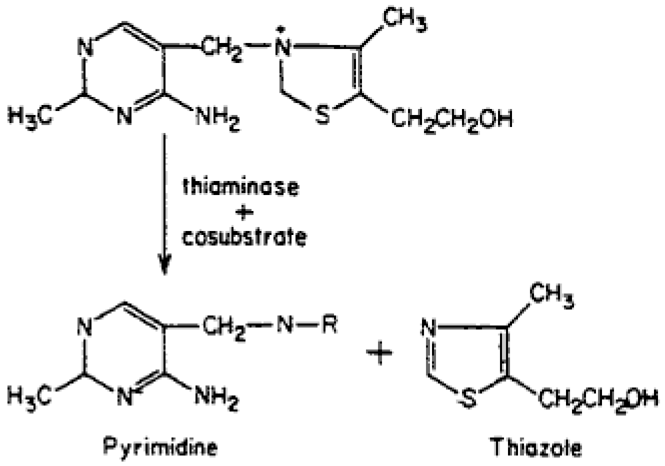
- Worldwide, especially forested areas, common where recently cleared, in abandoned fields, open woods, chiefly on dry sandy soils or gravelly areas.
- Often in dense stands.
- Has caused serious losses in the northeastern, southeastern, midwestern, and far western USA. Poisoning most commonly reported in Pacific Northwest and north central Midwest.

Toxic Principles

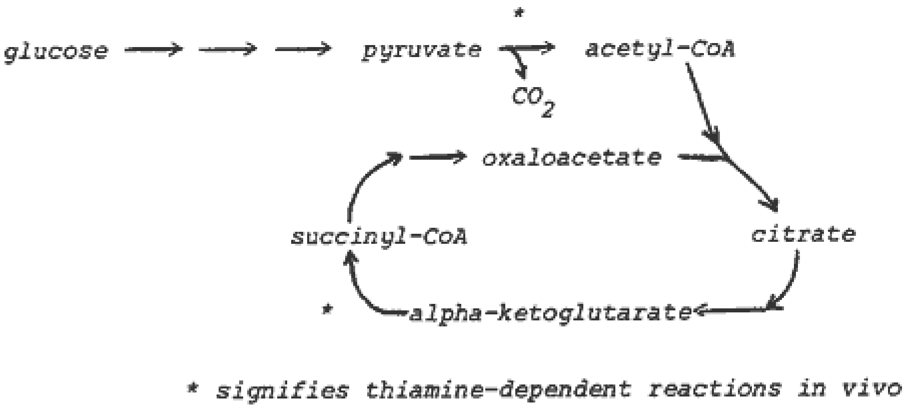
- Several toxic principles are recognized including:
    - Thiaminase.
    - A factor that damages the bone marrow.
    - Ptaquiloside (= aquilide A) is the suspected carcinogen in brackenfern.
    - Cyanogenic glycoside (significance not clearly established).

Mechanism

- Toxicity in horses (and rats) is due to a thiaminase (destroys thiamine in the digestive tract before it can be absorbed), resulting in central nervous system dysfunction and damage.



- Thiamine deficiency results in impaired pyruvate utilization. Blood pyruvate levels rise. Animal suffers from abnormal energy metabolism due to inadequate ATP production.



Normal role of thiamine in cellular metabolism

- Toxicity in cattle is due to an unidentified toxic principle and not thiaminase. At least part of the problem is due to a carcinogen.

Toxicity

- Poisoning may occur at any time of year, but is more often in late summer when other forage is depleted, or in winter when contaminated hay is fed. Levels of thiaminase in the plant peak in the late summer.
- Toxic principles (thiaminase and compound toxic to bone marrow) are present in both fresh and dried plant materials.
- Young plants and rhizomes are especially toxic.
- Generally, signs occur after significant consumption, such as after 1 month of eating hay containing 20% bracken.

Species Affected

- Cattle most commonly affected. Reports of poisoning in horses, swine, and sheep are less frequent.
- Seasonal tendency - Late summer to early fall.
- Horses and cattle are primarily affected, and the syndromes differ:
  - Horses - Mainly neurologic.
  - Cattle - Mainly bone marrow damage.
- Sheep and swine rarely eat bracken, but exposed swine (at least) may sometimes experience a thiaminase mediated syndrome.

Signs

- In the horse:
    - Horses generally must consume bracken fern for 1 - 2 months before the onset of clinical signs occurs. Clinical signs can also occur even when horse is no longer on bracken fern.
    - Emaciation.
    - Loss of weight occurs despite maintenance of appetite until the late stages of the disease.
    - Lethargy.
    - Incoordination, especially when forced to walk. Can progress to overt staggers - Occasionally referred to as "bracken staggers".
    - Wide stance, arched back, crouched stance.
    - Severe tremors, unable to arise, injuries from attempts to get to feet; most pronounced when attempt to work animal.
    - Bradycardia with arrhythmias seen early in disease course. Weak, fast pulse, terminally.
    - Convulsions, recumbency, and opisthostonus terminally. Hyperthermia also observed terminally.
    - Hemolytic crisis rarely reported.
    - If not treated, death in 2 - 10 days (occasionally survive up to 30 days or more after onset).
- In cattle:
    - Considered a "radiomimetic" disease in cattle and sheep.
    - Thiamine production in the rumen results in resistance to the thiaminase syndrome seen in horses.
    - Signs of poisoning begin 1 - 2 months after being turned into bracken containing pasture, or after being given bracken-containing hay.
    - Deaths have occurred at 7 - 8 weeks after first access. Acute course of illness-usually with death within 4 - 8 days of the first onset of clinical signs. Disease develops as a result of bone marrow suppression.
    - Early fever (106 - 108º F).
    - Loss of condition, anorexia.
    - Anemia (late).
    - Bracken fern-induced hematuria in cattle has been called bovine enzootic hematuria.
    - Leukopenia.
    - Thrombocytopenia, blood-tinged nasal discharges, bloody or "tarry" feces, blood clots in feces, hematuria. Prolonged clotting times, defective clot retraction.
    - Edema of larynx and dyspnea.
    - Differential diagnosis in cattle includes: septicemia, anaplasmosis, moldy sweet clover ingestion, and leptospirosis.
    - Bladder and upper gastrointestinal carcinoma in cattle exposed to bracken fern for 1 - 6 years.
- In swine:
    - Depressed growth rate, dyspnea, weakness, recumbency, and death.
    - Clinical signs are the result of thiamine deficiency.
    - Elevated pyruvate levels.

Diagnosis

- Evidence of significant ingestion.
- Appropriate clinical signs and lesions.
- Thiamine analysis of whole blood (avoid hemolysis) of monogastrics may help support the diagnosis. Contact Dr. Dwayne Hamar, Department of Pathology, Veterinary Diagnostic Laboratory, Colorado State University, USA.

Lesions

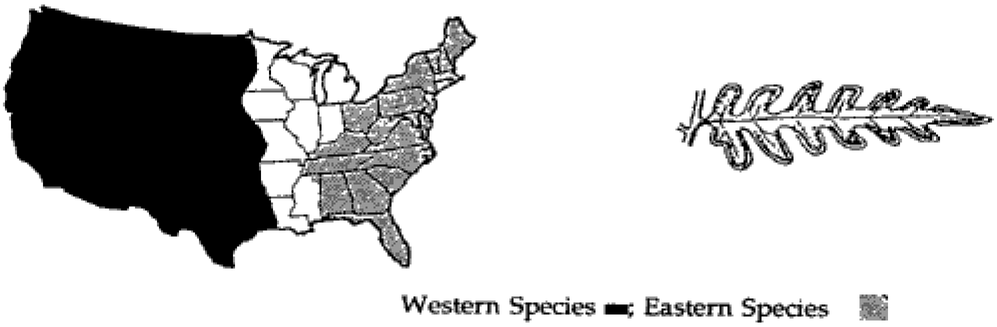
- In horses:
    - Enteritis, with some pericardial and epicardial hemorrhages.
- In cattle:
    - Generalized hemorrhages, anemia, aplastic marrow.
    - Ulceration of the abomasum.
    - Lesions in urinary tract most often involve the bladder. Lesions range from hyperplastic and hemorrhagic inflammation to frank neoplasias.
- In sheep:

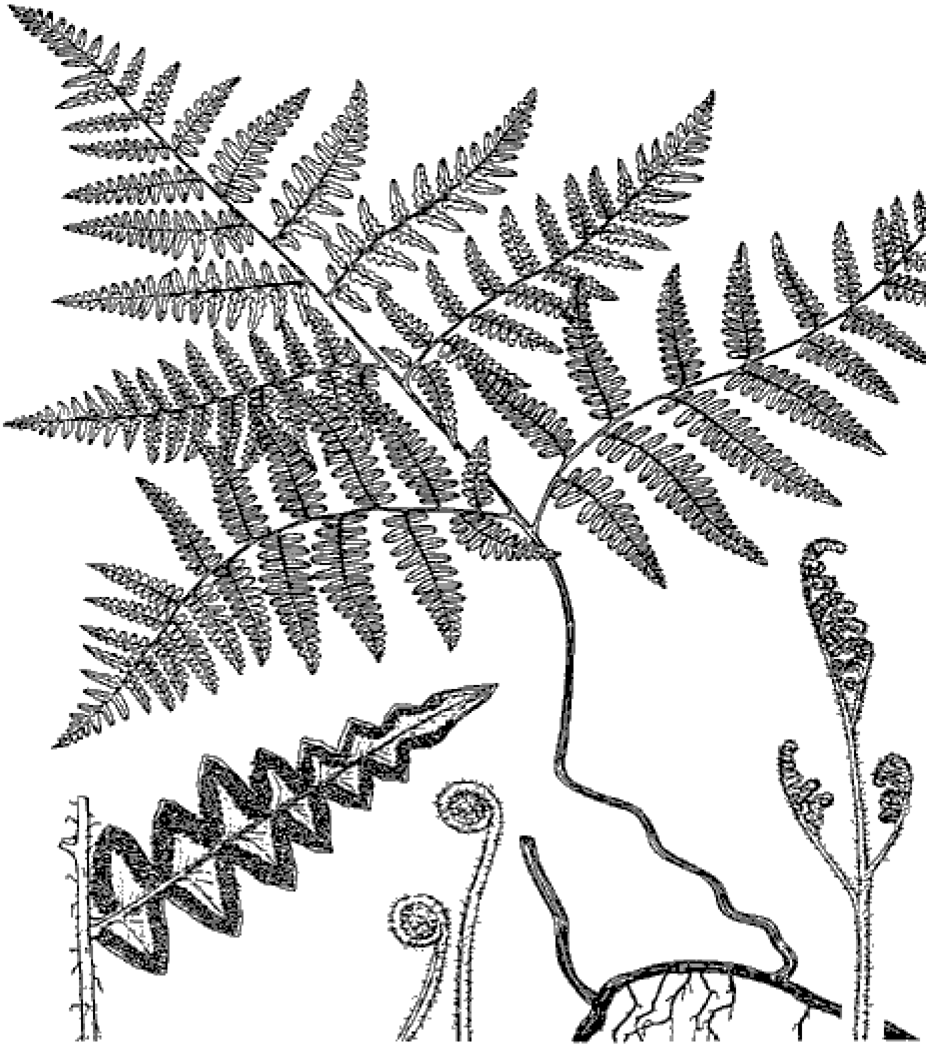
    - Great Britain-ingestion of bracken fern has been associated with retinal atrophy, "bright blindness". Characterized by loss of rods and cones and outer nuclear layers. Experimentally reproduced by feeding bracken to sheep.
    - Hemorrhagic syndrome similar to cattle.
- In swine:
    - Enlarged, mottled heart, congestive heart failure.
    - Lungs edematous, ascites, and enlarged gall bladder.
    - Degeneration of cardiac muscle fibers.

Treatment

- In horses:
    - Saline cathartic.
    - Activated charcoal.
    - Thiamine HCl - At a dose of 0.25 - 0.5 mg/kg, IV or IM, daily for several days, up to 2 weeks.
- In swine:
    - Treatment of swine is similar to that described for horses.
- In cattle:
    - Blood transfusions - 1 gallon per day at onset.
    - Broad spectrum antibiotics.
    - d,1-batyl alcohol: Treatment with d,1-batyl alcohol is not consistently effective.
        - Preparation of d,1-batyl alcohol for intravenous administration: add 5 grams of Tween-80 or Tween 20 emulsifier to 100 ml saline and dissolve in a water bath. After heating, add 2 grams of d,1-batyl alcohol and shake vigorously periodically until homogeneous. After cooling in cool water, the mixture should be only mildly opalescent. If not, reheat with shaking and cool again. This approximately 2% batyl alcohol solution may be given intravenously.
        - Preparation for subcutaneous administration: the concentrated alcohol may be diluted in olive oil at a rate of 1 gram batyl alcohol to 10 ml of the oil.
        - The dose administered is 1 gram of d,1-batyl alcohol intravenously or subcutaneously daily for five days. d,1-batyl alcohol available from Sigma Chemical Co., St. Louis, MO.
    - Protamine sulfate (1%), a heparin antagonist administered as a 10 ml injection, in conjunction with blood transfusions may be of benefit.
    - Phenothiazine added to the diets of mice and rats reduced the incidence of bracken fern-induced tumors. May be result of increased liver microsomal enzyme activity and subsequent metabolism. Questionable efficacy in ruminants (sheep) experimentally.

Major Areas of the Distribution of Bracken Fern. Spores on Underside of Fronds





Bracken Fern. Note the large pinnately divided leaf-like frond, the spore-bearing frond (lower left), fiddleneck (lower center), unfolding fiddleneck (lower right), and the underground rootstock (lower right) of this primitive plant.

Equisetum Arvense - Horsetail

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Thiaminase-Containing Plants and Other Substances
Horses	Weeks to months	Weeks to permanent damage; potentially lethal	

Synonyms - Scouring rush, marestail, and jointed rush

Description

- Perennial herb, very short or up to 4 feet tall.
- Hollow stems-green, segmented.
    - Harsh in texture due to large amount of silica.
    - Stems readily separate at segmentations (nodes).
- Leaves-vestigial in whorls at the nodes.

Habitat

- Native - Midwest - West - All USA - Especially cooler areas.
- Moist, wet areas.
    - E.g., meadows, along ditches, ponds, etc.
    - Tolerates soils low in fertility.
    - Low lying areas in pastures and fields.

Toxic Principle

- Thiaminase in nonruminants.
- Unknown in ruminants.
- Remains toxic when dried.

Susceptible Species

- Horses primarily affected, especially younger animals.
- Rarely cattle, sheep.
- Poisoning on pasture, but mostly in winter when contaminated hay is fed.

Diagnosis (See Bracken Fern [*Pteridium*])

Signs

- Clinical signs develop after eating several days-onset is characterized by a loss of weight.
    - Weight loss becomes chronic with continued ingestion.
- The syndrome progresses at a rate dependent on intake.
- Signs of a nervous disorder and muscular weakness.
- After approximately 1 month, incoordination may affect hind limbs first.
- At 40 - 45 days, paresis occurs and continued ingestion results in convulsions and death within 1 - 15 days. Progressive muscular rigidity.
- Tenesmus and constipation marked.

Lesions

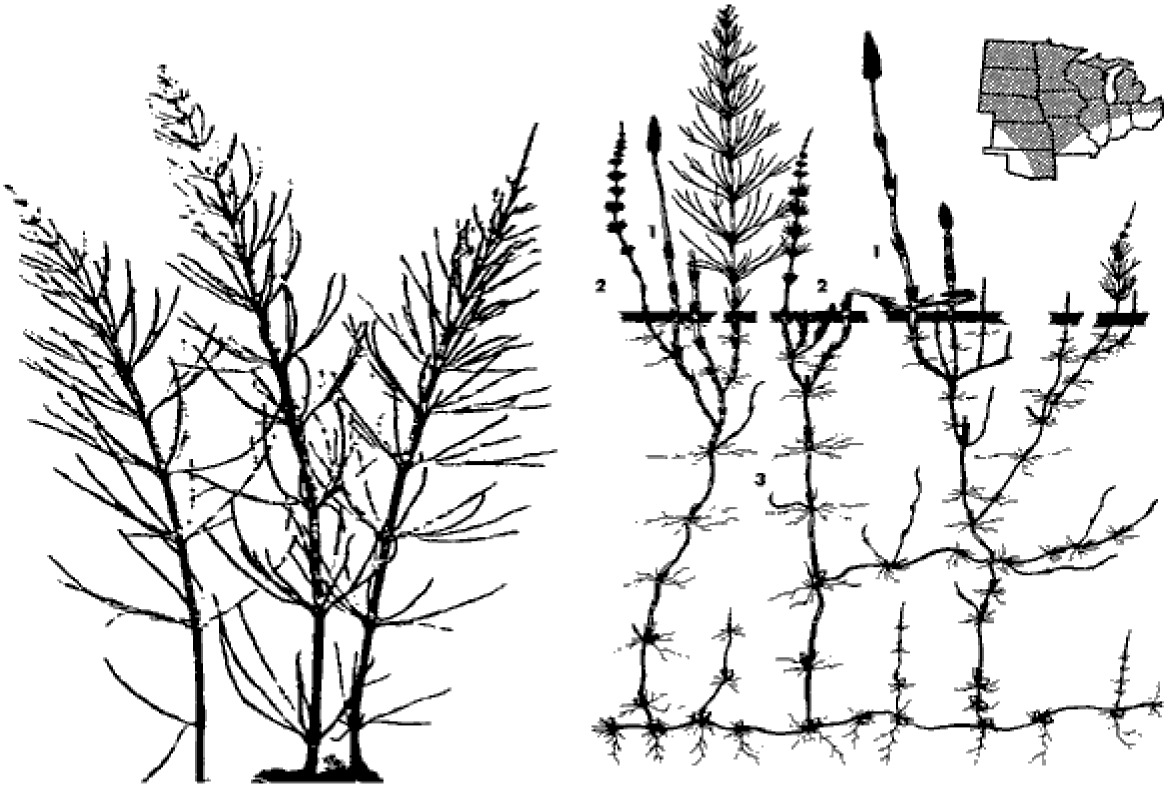
- Pale and flabby skeletal musculature.
- Hydroperitoneum, congestion, and inflammatory edema of the meninges.
- Congestion of lungs, proximal renal tubular epithelial degeneration.

Treatment

- Remove from source.
- Supplement with good diet.
- Inject thiamine HCl at 0.25 - 0.5 mg/kg IV or IM for several days.

Prognosis

Favorable unless the animal is unable to arise at outset.



Field Horsetail, *Equisetum arvense* L. **1**, fertile or reproductive shoots; **2**, sterile or vegetative shoots; **3**, rhizomes. **Perennial**, reproducing by spores instead of seeds, and by rhizomes, to which are attached small tubers. **Stems** tough and wiry, hollow, jointed, and of two types: *fertile*, producing fruiting heads and having large, easily separable joints, not branched; *sterile or vegetative*, having much smaller joints, with lateral branches in whorls around the main stem. **Leaves** on sterile stems only, in the form of cupshaped toothed sheaths at the joints. **Fruiting heads** contain masses of tiny pale greenish spores in small pine-cone-like structure. **Found** mostly on wet, sandy, or gravelly soil. It is poisonous to livestock when eaten in large quantities. There are several species of *equisetum* in the area, all of which can be recognized as horsetails from this illustration.

Thiaminase and Thiamine (Vitamin B_1) Deficiency in Cats, Dogs, Fur-Bearing and Marine Mammal Species

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Thiaminase-Containing Plants and Other Substances
Cats, dogs, foxes, mink, captive marine mammals	Weeks	Days to permanent damage; potentially lethal	

Introduction

Thiamine (vitamin B_1) deficiency occurs in cats fed all fish diets that contain thiaminase, and occasionally dogs fed cooked meats (cooking can destroy thiamine). Occasionally, it occurs in chronic anorexia, or extensive diuresis without vitamin supplementation (especially in cats which have higher thiamine requirements than dogs).

Sources

- Many kinds of fish, from both fresh and salt waters, e.g., carp, catfish, smelt, whitefish, white bass, herring, and others, include thiaminase.
- Thiamine may also be destroyed by excessive heating or prolonged storage of foods.

Mechanism of Action

See Bracken fern handout.

Susceptible Species

- Cats, dogs.
- Mink (Chastek paralysis), foxes (Chastek paralysis), seals, sea lions, bottle-nose dolphins, etc.

Clinical Signs

- Thiamine deficiency predominately affects the nervous, gastrointestinal, and cardiovascular systems.
- In the earliest stages, cats develop anorexia, salivation, vomiting, and weight loss. Ataxia and dyspnea may develop.
- Other clinical signs include a mild vestibular ataxia (frequently asymmetrical, no loss of strength, circling, falling, or tipping toward the side of the lesion). Sometimes signs of acute vestibular disturbances accompany a prolonged period of inappetence, and complete remission of signs follows thiamine therapy.
- Cats may also develop circling, dysmetria, dilated pupils, and hypersensitivity.
- Generalized convulsions frequently are elicited by handling the cat. Convulsions in cats are characterized by kyphosis (ventroflexion of the head), hyperesthesia, and unresponsive pupils. Seizures are often generalized and are "grand mal" and of short (< 30 seconds) duration.
- Occasionally, retinal hemorrhages occur.
- Cardiovascular abnormalities in the cat include bradycardia or tachycardia with arrhythmias.
- Pupils may be dilated and poorly responsive to light.
- Terminally, there is semicoma, continual crying, opisthotonus, and persistent extensor tonus. Can develop 3 - 4 days after the initial clinical signs.
- Dogs develop upper motor neuron paraparesis that progresses to tetraparesis and convulsions. Dogs have persistent anorexia, with paraparesis developing several days after the onset of anorexia.
- Thiamine deficiencies in nondomestic carnivores can produce a dry, unkempt coat, and paralysis. The condition is also known as Chastek paralysis in the fox.

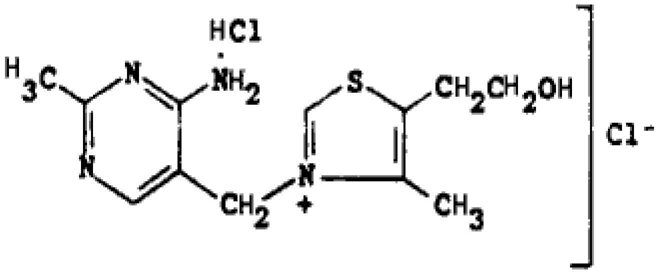
Lesions

- Symmetric periventricular polioencephalomalacia is the characteristic lesion in thiamine deficiency. Lesions can vary in severity from bilateral spongy change to frank necrosis.
- Unlike hypoxia, and some toxin-induced changes, these lesions are primarily located in the brainstem. Terminally, there is a bilaterally symmetrical hemorrhagic necrosis of the brain stem periventricular grey matter, which includes lateral geniculate nuclei, oculomotor nuclei, and vestibular nuclei.
- Cats may also have ulceration of the mucosa of the pylorus.
- Generalized vascular dilatation including retinal, brain, and spinal cord vasculature.

Diagnosis (See Bracken Fern [*Pteridium*])

Therapy

- Treatment for thiamine deficiency should be instituted in any animal in which it is suspected based on history and clinical signs.
- Therapy with 2 mg/kg/day of thiamine hydrochloride (IM) early in the disease will generally result in clinical improvement. A single dose of 250 mg was tolerated and effective in a thiamine-deficient border Collie.



Thiamine HCl (Vitamin B_1)

- Thiamine deficiency also occurs naturally in mink as well. Has been described in captive seals, sea lions, and bottle-nosed dolphins

Toxicants that Cause Central Nervous System Depression

V. Beasley

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Eupatorium rugosum - White Snakeroot

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Cattle, horses, sheep, goats	Days to weeks	10 - 14 days in cattle; permanent heart damage in horses; often lethal in both species	

Synonyms - Richweed, white sanicle

Description

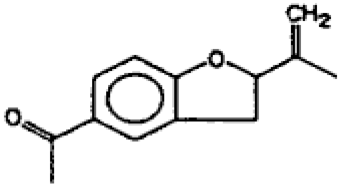
- An erect, herbaceous perennial with stiff, branched or unbranched stems, mostly 3 - 4 feet tall. Grows from a shallow mat of fibrous whitish roots. Leaves are opposite, 3 - 6 inches in length, with serrated margins, and 3 ribs. Leaves get larger as you move down the stem.
- Flowers are white, small, in composite heads of 10 - 30 flowers at the top of the plant. Although it is fairly easy to identify, similar nontoxic species of *Eupatorium* do exist, therefore, confirmed identification by a botanist is recommended.

Habitat

- Open-wooded, semi-shaded areas, especially common at the edge of the woods, from eastern North America westward to Minnesota and Texas.
- Most severe problems in southern Ohio, Indiana, and Illinois, as well as in eastern Missouri and North Carolina.

Toxic Principle

- The apparent toxic principle in white snakeroot has been given the trivial name, tremetol, and has been described as a fat soluble, high molecular weight alcohol.
- Crude tremetol, was later shown to be separable into a toxic ketone fraction (61%) (tested in goldfish) and a sterol fraction (39%), which was nontoxic. The ketone fraction was later separated into tremetone, dihydrotremetone, and hydroxytremetone. These may all be components of a fragile tremetol molecule, however, the identity of the toxic principle remains to be clarified. For the purposes of this course and state board exams, it should be assumed that tremetol is the toxic principle in white snakeroot.



Tremetone

Toxicity

- The toxic substance remains in the dried plant after frosts. The toxic principle is a cumulative poison and repeated exposure to small amounts results in intoxication.
- The toxin is secreted in the milk apparently far more rapidly than by any other route which can result in relay toxicosis to offspring or humans.

- No reliable test for the presence of tremetol is presently available.
- It generally stays green and succulent in dry weather and after the first frost, so that more consumption and more poisoning occurs at those times.
- Reported that ingestion of 1 - 10% of an animal's body weight of green plant may be lethal to cattle, sheep, and horses, whether ingested at 1 time or with smaller successive doses.

Susceptible Species

- Cattle, horses, and sheep are most commonly poisoned. Goats appear to be particularly sensitive.
- Suckling calves are especially at risk; at least in cattle, lactating animals are significantly protected. Thus in cattle, beef calves are most often affected.
- Nonlactating, grazing animals are also affected.
- "Milksickness" was a major problem in humans during the period of westward expansion, reportedly caused the death of Abraham Lincoln's mother. Pasteurization does not detoxify milk; but dilution in modern dairies apparently provides a large safety factor.

Signs and Effects

- In cattle:
  - Stiffness, apparent severe CNS depression, unsteadiness, ataxia, sternal recumbancy, anorexia, and weight loss. Animals develop tremors especially of the flank, neck, hind legs, and face which become more severe with exercise. Later complete relaxation without tremors, coma, and frequently death.
  - Occasionally constipation, salivation.
  - Syndrome persists for at least 10 - 14 days after removal from white snakeroot and weaning.
  - Ketoacidosis may be a major feature in some cases (acetone odor to breath and urine in some animals).
  - Deaths occur within 2 - 10 days.
- In horses:
  - Onset of clinical signs within 2 days to 3 weeks after ingestion (usually after at least several days of ingestion).
  - Congestive heart failure.
  - Stand with legs wide apart.
  - Swelling of ventral neck near thoracic inlet.
  - Jugular pulse, tachycardia.
  - EKG changes include increased rate, ST elevation, and variable QRS complexes, e.g., ventricular premature beats. Auscultable cardiac arrhythmias are often present.
  - Sweating, especially between rear legs.
  - Tremors are inconsistently observed.
  - Stumbling (in rear legs) when turned in some instances. Severe depression can occur.
  - Hematuria may occur.
  - Choke sometimes occurs.

Clinical Pathology

Horse, elevated CPK, SGOT, SGPT, and SAP.

Lesions

- In cattle:
  - Fatty liver, congestion and degenerative changes in liver. Hemorrhage of variable extent may be found in the heart and GI tract.
- In horses:
  - Myocardial degeneration, necrosis, and fibrosis. Straw-colored fluid in pericardial sac. Extensive pale areas of the subendocardium.
  - Ventral edema.
  - Centrilobular degeneration with mild necrosis and fatty changes, possibly due to cardiac insufficiency.

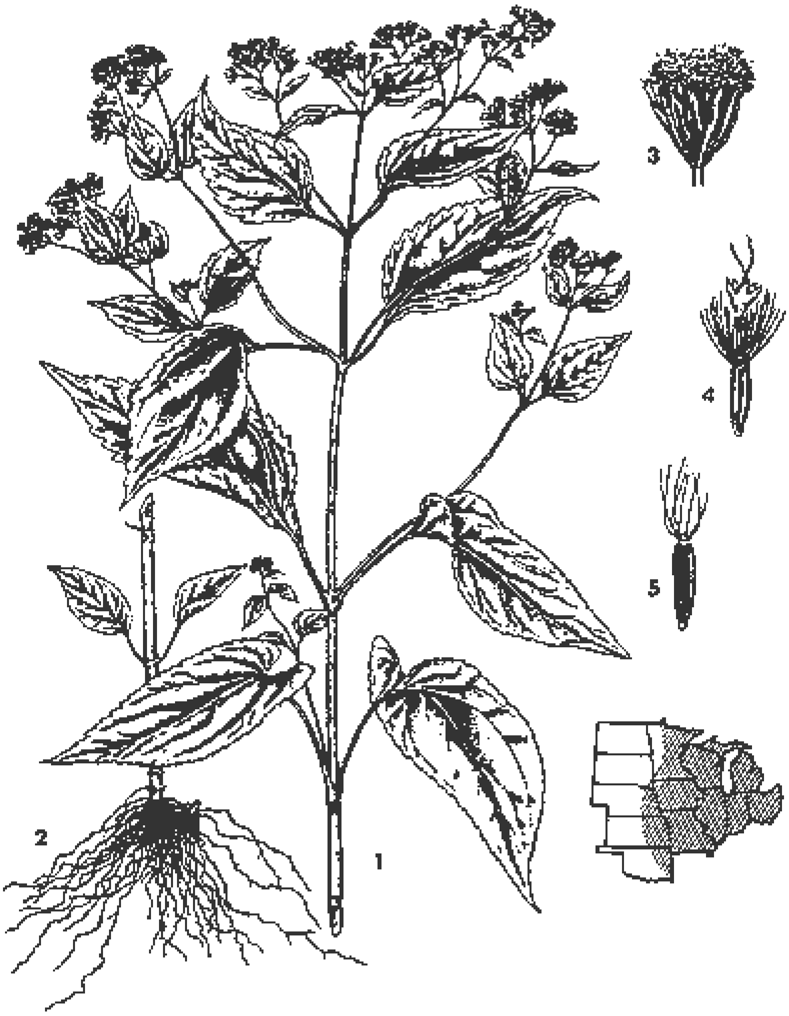
Diagnosis

- Characteristic clinical signs.
- History of exposure to white snakeroot.

Treatment

- No studies involving therapy are known to have been conducted.
- Treatment is therefore empirical.
- In cattle:
    - Activated charcoal and if hydration is adequate a saline cathartic. Dry bedding, good shelter, good nursing care. Provide feed and water in such a way that animals can consume them (i.e., put under animals nose if necessary). Consider need for fluids, B-vitamins, and tube feeding. Monitor for secondary infections, etc. May require treatment for ketosis. If possible, continue to milk animals to enhance excretion; dispose of milk.
- In horses:
    - Activated charcoal, saline cathartic. Monitor arrhythmias and EKG: treat symptomatically. May be left with severely scarred heart, and associated circulatory dysfunction. Fecal softeners.
    - Symptomatic and supportive therapy.

Composite Family, *Compositae*



White Snakeroot, *Eupatorium rugosum* houtt. **1**, upper part of plant; **2**, root; **3**, flower head; **4**, single flower; **5**, seed. **Perennial**, spreading by seeds and short rhizomes. **Roots** much branched and fibrous. **Stem** 1 to 3 feet (30 - 90 cm) tall, smooth, and branched near top. **Leaves** opposite, elliptical, thin, smooth, with toothed edges and slender petioles. **Flower heads** small, of white disk flowers only. **Seed** black, angular, about 1/8th inch (3 mm) long, with a tuft of white hairs. **Found** in hardwood timber areas, woodland, pastures, and waste places. It grows only in shaded areas. Contains a cumulative poison that causes the disease known as "trembles" in cattle and horses. Dairy products from animals that have eaten the plant are poisonous to man, causing "milk sickness", one of the main scourges of pioneers in the region.

Isocoma wrightii - Previously *Haplopappus* or *Aplopappus* - Rayless Goldenrod

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Central Nervous System Depression
Herbivores, esp. goats	Days to weeks	Days to weeks; potentially lethal especially in goats	

Synonyms - Jimmyweed, burrow weed

Description

- An erect, bushy, unbranching, perennial shrub, that grows 2 - 4 feet tall.
- Leaves are alternate, linear and sticky, and the flowers are terminal and yellow.

Habitat

- Dry range lands of southern Colorado, western Texas, and most of northern Mexico and Arizona.
- Grows especially in river valleys and along drainage areas. Abundant along the Pecos River.

Susceptible Species and Poisonous Principle

Affects horses, cattle, sheep, and goats. Young are poisoned because the toxic substance, reportedly tremetol, is secreted in the milk. Severe losses have occurred in livestock; milk sickness in nursing animals and humans.

Toxicity

Ingestion of 1 - 1.5% of bw of *I. wrightii* during a 1 - 3 week period may cause toxicosis in cattle, sheep, and horses.

Clinical Signs

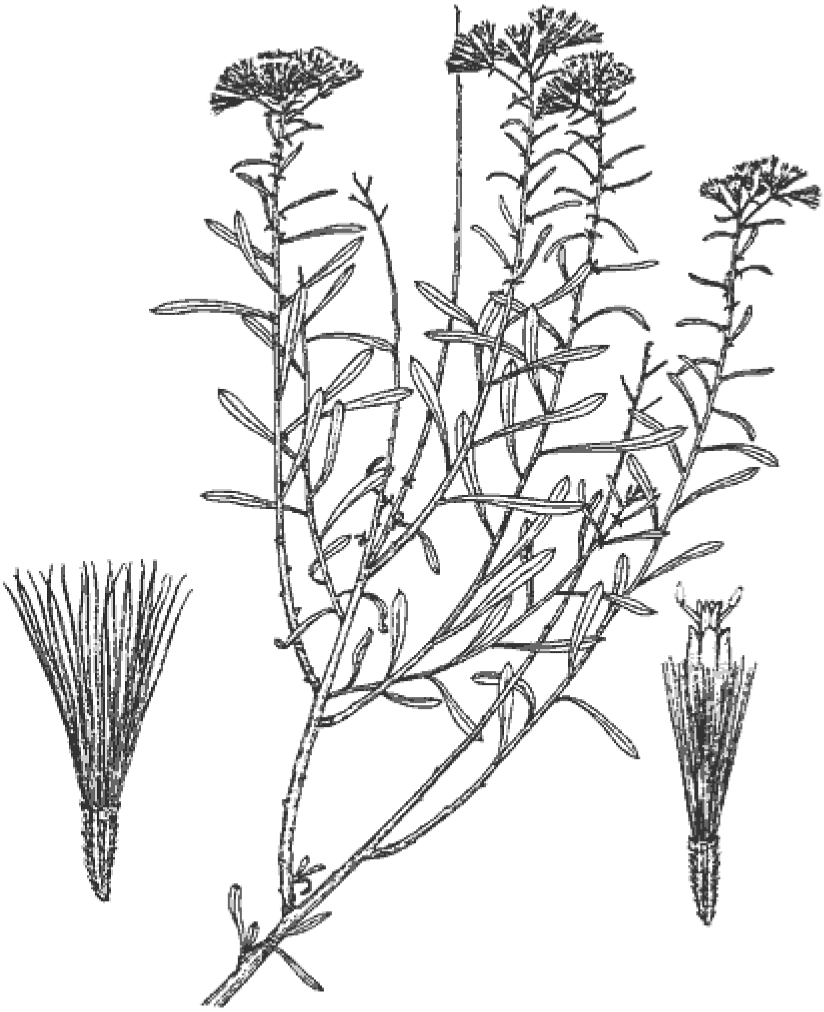
- Cattle.
  - The syndrome in cattle is similar to that which occurs in white snakeroot poisoning; however, the tremors that occur may be much more severe.
  - Rear limb weakness, knuckling of fetlocks, can progress to posterior paralysis.
  - Acetone odor on breath from ketosis.
  - Urinary incontinance and constipation.
  - Skeletal muscle damage may be extreme and elevations of CPK may be marked. Elevation of SGOT and LDH also occurs.
- Horse.
  - There is no documentation of heart muscle degeneration of horses as occurs in white snakeroot poisoning.

Lesions

- Centrilobular necrosis of liver.
- Congestion of brain and spinal cord.
- Congestion and fatty degeneration of liver and kidneys.

Diagnosis

- Clinical signs.
- History of exposure.



Isocoma wrightii. The narrow pointed leaves, the clusters of yellow flower heads at the tip of the branches, and the flower (enlarged, lower right) and fruit (enlarged, lower left) with its crown of bristles characterize this plant.

Opiates and Opioids

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs, cats	Minutes to hours	Hours to 2 days	

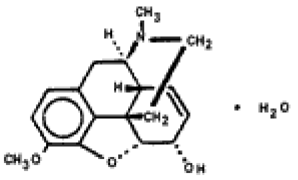
General Statements

- Rare cause of poisoning in dogs and cats.
- Dogs - Several agents used in dogs as analgesics; apomorphine used as an emetic.
- Cats - Extreme stimulation with some agents such as morphine-therefore not used except at a very much lower dose than in the dog. Apomorphine-no safe and reliable dose in cats established in spite of attempts to find one. Demerol (meperidine) is sometimes used in the cat as an analgesic at 2 - 4 mg/kg, IM, SC (not as an emetic).

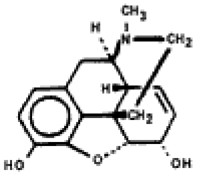
- Morphine used in treatment of pulmonary edema (cardiogenic and neurogenic pulmonary edema); but not for use with pulmonary edema from chemical irritants.

Sources

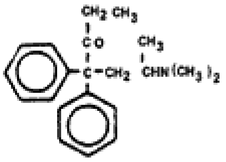
- Most opiates available in both oral and parenteral forms, both legally and illicitly.
- Morphine - Analgesic; some use as an emetic in dogs.
- Etorphine (M99), a derivative of the opium alkaloid thebaine, used for immobilization of wild-life and is 80 - 1000 times more analgesically potent than morphine. Diprenorphine M50 - 50 is an etorphine antagonist.
- Paregoric - Camphorated tincture of opium.



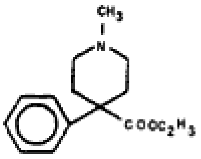
Codeine



Morphine



Methadone



Meperidine

Phenanthrene Derivatives **Diphenylheptane Derivatives** **Phenylpiperidine Derivatives**

Chemical Types

- Opiates are classified into three general groups based on chemical structures, namely:
  a. Phenathrene derivatives including morphine, codeine, and oxymorphone;
  b. Phenylpiperidine derivatives including meperidine and fentanyl; and
  c. Diphenylheptane derivatives of which methadone is the only commercially available forms.

Mechanism of Action

- Interact at opiate receptor sites in the CNS and other tissues. Several subtypes of opiate receptors have been described including m-receptor (pain centers CNS), a receptor (cerebral cortex), w receptor (limbic system, and the s receptor (CNS).
- Opiate interaction with receptor populations varies with each specific opiate agonist.
- Precise mechanism of action producing analgesia is not fully understood.
- Result in suppression of cough reflex, respiratory depression, behavioral changes, and CNS depression.
- Produce miosis, decrease GI motility by an unknown mechanism. Also result in increased urinary sphincter tone which can result in dysuria.
- Produce hypotension by causing peripheral vasodilation.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Variable absorption following oral administration.
- Onset and duration of signs varies with each particular opiate.
- Cross placental barrier, can cause fetal depression.
- Primarily metabolized in the liver by glucuronidation (deficient in cats), hydrolysis, and oxidation; excretion of glucuronide derivative in the urine.

Common Opiates and Opioids - Key Differences

- Morphine - Limited penetration of the brain.
- Codeine - Weak action at opiate receptors; action may be due to conversion to morphine in the body.
- Heroin (diacetylmorphine) is rapidly hydrolyzed to monoacetylmorphine which is hydrolyzed to morphine. Heroin more readily penetrates the blood brain barrier as compared to morphine. Elimination same as morphine.

Predisposing Factors

- Increased susceptibility to respiratory depression in:
    - Old patients and neonates.
    - Hypothyroid patients.
    - Hypothermic animals.
    - Liver disease.
    - Patients with reduced blood volume.
- Contraindicated in head injury.
    - The narcotics may increase intracranial pressure plus increase the tendency for respiratory depression to occur.
- Contraindicated with seriously decreased respiratory depression from any cause.
- Hypotension may be aggravated by concurrent exposure to phenothiazine tranquilizers, monoamine oxidase inhibitors or tricyclic antidepressants.

Toxicity

- Lethal SC or IV doses morphine in dog 110 - 220 mg/kg.
- Meperidine (Demerol) can produce excitement and convulsions in the cat when administered at 20 - 30 mg/kg.
- Propoxyphene hydrochloride (Darvon) at 40 mg/kg PO in dogs produced tremors, salivation, ataxia, and vomiting. Lethal effects produced at 125 mg/kg.
- Pentazocine lactate (Talwin) administered at 6 - 10 mg/kg IM in the dog and 2.2 - 4.4 mg/kg IM in the horse produced ataxia, tremors, and convulsions.

Signs

- CNS depression, vomiting, ataxia, and respiratory depression are commonly observed.
- Coma, cyanosis, and poor perfusion are seen in later stages. Bradycardia and arrhythmias may occur.
- Miosis, but if severely hypoxic, mydriasis can occur. Mydriasis more commonly seen with meperidine overdoses in human patients.
- Hypothermia.
- Flaccidity of muscles.
- Convulsions occasionally seen.
- Pulmonary edema and pneumonia may also develop.
- Death due to respiratory failure, or later due to shock.

Diagnosis

- Clinical signs.
- History of exposure.
- Response to naloxone 0.01 - 0.02 mg/kg. If no improvement after 1 - 2 doses, reconsider the diagnosis.

Treatment

- Airway-assist respiration, or artificial respiration. O_2 therapy.
- Narcotic antagonist:
    - Duration of effect of antagonists is often less than that of the opioid. Antagonist must, therefore, be repeated to avoid subsequent severe depression. Antagonists, such as nallorphine or levallorphan may exert depressant effects, whereas nalloxone does not have this disadvantage.
    - Nalloxone, drug of choice, at 0.01 - 0.02 mg/kg is administered IV, IM, or SQ in the dog or cat.
- Oral exposure - Evacuate gastrointestinal tract, activated charcoal and saline cathartic.
- Gastric lavage and activated charcoal may be effective even many hours after ingestion since opiate-induced pylorospasm may be present.
- Nalozone has been reported to not prevent meperidine (Demerol) - induced seizures. Treatment with phenobarbital was successful in antagonizing lethal convulsive effects of meperidine.

Note

Opiate agonists are subject to control under the Federal Controlled Substances Act of 1970.

Cannabis sativa - Marijuana

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs, rarely cats	Minutes to hours	One to 2 days; unlikely to be lethal	

Synonyms - Marijuana, hemp, pot, grass, Mary Jane, sensemilla.

Hashish is a concentrated, dried resinous form of marijuana that sometimes may contain other (added) drugs.

Description

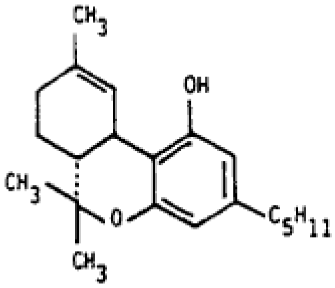
Marijuana is a tall, coarse annual herb in the hemp family; introduced from temperate Asia. The leaves are long-stalked and palmately divided into 3 - 7 narrow, pointed, toothed leaflets. Flowers are small, green, and clustered in the leaf axils. Male and female flowers are on separate plants. Flowers, leaves, and stems are covered with hairs which exude a sticky resin.

Habitat

It is a widely naturalized weed in temperate North America and is cultivated in warmer regions.

Toxic Principle

The toxins are various resins, mainly THC (tetrahydrocannabinol) and related compounds. Canabinoid is a C_{21} compound, carboxylic acid. Analogs include W^9-trans-tetrahydrocannabinol (WTHC), the most active constituent on the CNS in cannabis.



Structure of THC

Toxicity

- Not considered a poisonous plant if consumed fresh, becomes poisonous when damaged by drying, heating, smoking, and/or aging.
- The entire plant is toxic, especially the leaves, flowering parts, sap, and resinous secretions.
- The amount of resinoid in the various plant parts varies with plant variety, sex of plant (female plant, "sensemilla" more toxic), geographic location, and growing season.
- Toxic substances are highest in plants grown in warm climates or seasons.
- Poisoning may result from drinking the extract and chewing or smoking the plant parts. Effects of these plants have been known for more than 2,000 years.
- Effect of marijuana can be related to THC content to some extent.
- Hashish is a concentrated form of marijuana. Sometimes hashish contains added opium.
- Oral LD_{50} W^9-THC rat 661 mg/kg, mice 482 mg/kg.
- Minimal lethal oral dose monkeys and dogs ≥ 3 g/kg.
- Plants can contain 1 - 6% THC, extracts as much as 28% THC.

Signs and Symptoms (Humans)

- THC is a CNS depressant with biphasic clinical signs: euphoria followed by depression.
- Exhilaration, delusions, mental confusion, dilated pupils, blurred vision, poor coordination, weakness, stupor, hallucinations, and coma (with large doses).
- Death may result from its depressing effect on the heartbeat.
- Other symptoms include craving for sweets, increased appetite, dryness of mouth, inflamed eyes, anxiety, aggressiveness, sleep disturbance, tremors, decreased sexual potency, feeling of contentment, increased but faulty perception and imagination, loss of initiative, reduction of will power and concentration, and impairment of lung function.

Signs (Small Animals)

- Ingestion by dogs and rarely cats causes ataxia, vomiting, mydriasis ("glazed eyes"), nystagmus, depression, and sometimes coma. Hypothermia in small animals has been demonstrated and may be dose related.
- Tachycardia or more commonly bradycardia.
- Prolonged depression for 18 - 36 hours is not unusual in marijuana-poisoned dogs.
- Occasionally animals may act hyperexcitable.
- Less frequently reported signs include tremors and salivation.

Comments

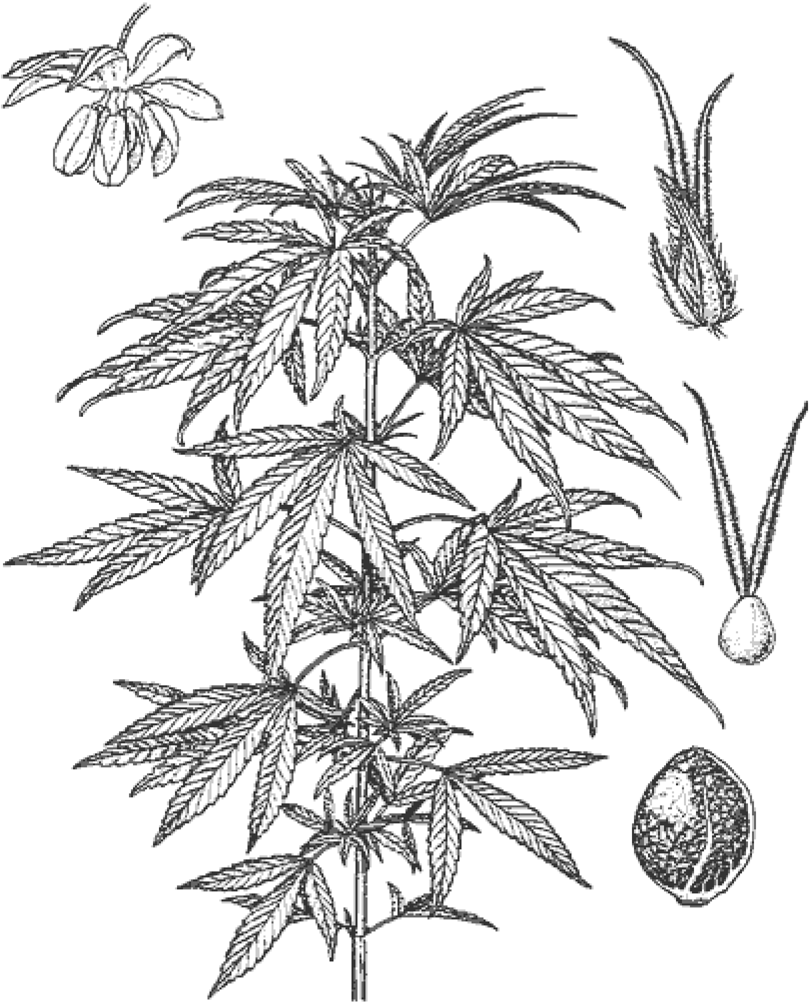
- The inner bark contains the tough hemp fibers used in making rope, the fruits are used as bird seed and to produce a useful drying oil, and the dried flowering and fruiting tops are a source of drugs.
- Federal (and state) laws prohibit the possession of living or dried parts of marijuana both in the United States and Canada.

Diagnosis

- Clinical signs.
- History of exposure. The owner(s) may be hesitant to provide the necessary information. Probing questions may be required.

Treatment

- Antiemetic properties may limit the effectiveness of emetic drugs but these may be tried prior to the onset of sedation or ataxia.
- Activated charcoal and a saline cathartic solution.
- Assist respiration if significant respiratory depression occurs.
- Haloperidol has been used to treat human beings with delusions or hallucinations.
- Diazepam has been used to treat people with marijuana associated anxiety and panic.
- Recovery may be slow (up to a few days) but may be hastened by detoxification of the digestive tract.



Marijuana (*Cannabis sativa*) - Note the palmately divided toothed leaves, the male flower (upper left), the female flower (upper right), the female flower with bracts removed (right center), and seed (enlarged, lower right) of this controversial drug plant.

Ivermectin and Milbemycin

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs (esp. Collies), cats, foals	Hours to a day	Days to weeks; potentially lethal	

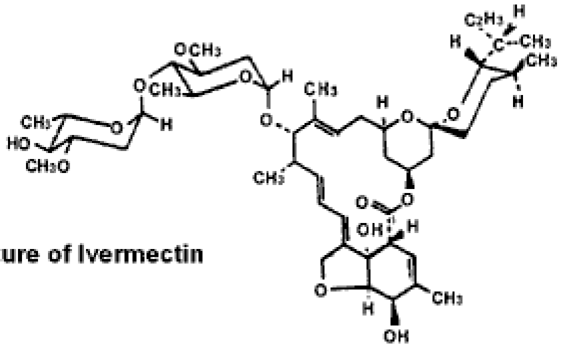
Introduction

- 22,23-dihydroavermectin B_1.
- One of the class of avermectins, which are polycyclic lactones.
- Fermentation product of *Streptomyces avermitilis*, a soil fungus discovered in Japan.

Available Forms (Sources)

- Heartgard 68 mcg, 136 mcg, 272 mcg sizes (tablets).
- Ivomec - Injectable 10 mg/ml (1%) (suspension) for cattle and swine.
- Eqvalen - Paste 1.87% - Now on the market for horses.
- Zimecterin - Paste (OTC) 1.87%, now on the market for horses.
- Eqvalen Injectable (pulled off the market in 1984 because of *Clostridial myositis* in 1 - 1.5 horses out of 100,000 horses given an injection).

  - Contained polysorbate 80 (Tween 80), a known histamine releaser in dogs (polysorbate 80 is also in other drugs; such as Konakion, a Vitamin K1 product.
- Interceptor ® tablets, containing milbemycin (another avermectin), are used in dogs for heartworm and hookworm control and occasionally for control of generalized demodecosis (an extra-label use).


Structure of Ivermectin

Toxicity

- Cumulative toxicity possible.
- Varies with species, breed, and age of animals.
- Younger animals appear more susceptible.
- Dogs.

	Single Oral Concentration	Clinical Signs
Beagles	2.0 mg/kg (2,000 µg/kg) 2.5 mg/kg 5.0 mg/kg 40.0 mg/kg	None Mydriasis Tremors Death
Collies	< 50 µg/kg 100 µg/kg - 200 µg/kg	None Tremors, mydriasis, and death

- Cattle and sheep oral ivermectin ≥ 4,000 - 8,000 mg/kg produced ataxia, depression.
- May result in death of migrating *Hypoderma* sp. larva.
- Signs occasionally delayed for 2 - 3 days in any species.

Susceptible Species

- Collies are apparently extremely susceptible to ivermectin.
  - 100 µg/kg is a dose that will have some clinical effects in some collie dogs.
  - 200 µg/kg will cause 30 - 40% to be markedly ataxic and some will go into a coma.
- Poisoning also occurs in shelties, border collies, and other related breeds which also appear to be predisposed.
- Milbemycin has been shown to have a similar therapeutic index to that of ivermectin, and dogs sensitive to ivermectin (especially collie-type breeds) are also sensitive to milbemycin.
- Poisoning occasionally occurs in other breeds of dogs as well.
- Apparently, similar toxic reactions sometimes occur in horses.
- Reactions to dead or dying parasites: (*Onchocerca* microfilaria in horses) die causing subcutaneous reactions, esp. ventral midline edema, colic in horses. In dogs may cause anaphylactic shock from microfilarial die off (controversial).
- Ivermectin ingestions have been associated with paresis and flaccid paralysis in chelonians = red-footed tortoise (*Geochelone carbonaria*) and leopard tortoise (*G. pardalis*). Toxicosis observed at 0.1 mg/kg or less.

Mechanism

- GABA mediation at inhibitory interneurons in mammals occurs only in the CNS; whereas GABA acts peripherally in invertebrates.

- Avermectins increase the activity of GABA receptors in 3 ways:
    1. Avermectins potentiate GABA effect at synapse by stimulating the presynaptic release of GABA.
    2. Avermectins enhance binding of GABA to postsynaptic receptors.
    3. There are also direct GABA agonist effects.
- GABA, the inhibitory neurotransmitter, opens postsynaptic chloride (Cl^-) channels allowing a Cl^- ion influx which causes an inhibitory effect through membrane hyperpolarization.
- Increase in Cl^- ion concentration inside the postsynaptic motor neuron causes retention of a negative charge (low electrical resistance), and subsequent excitatory or inhibitory signals are no longer registered by the recipient cell.
- This contrasts with the excitatory effects of acetylcholine which, instead, allows Na^+ ions to enter.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Active after oral or parenteral exposure.
- Generally the blood brain barrier (BBB) of mammals excludes ivermectin such that the host animal is unaffected by reasonable doses. In collies, the blood-brain barrier is ineffective as an ivermectin barrier. Blood-brain barrier deficiencies have also been postulated in chelonians and some affected horses. In any species, sufficiently high doses can overcome the ability of the BBB to exclude ivermectin from the CNS.
- Parent compound is persistent in the body which may explain, in part, the duration of effects (up to several days) seen in poisoned dogs.
- Excreted in the feces. Low degree of liver metabolism.
- Concentrated in liver and body fat.
- Low GI absorption. Peak plasma concentrations are reached 3 hours after oral administration.
- The half-life in dogs was reportedly 2 - 3 days.

Signs

- Horse.
    - Polysorbate 80 reactions (histamine release) are no longer a significant problem since the equine injectable product is no longer available. Ventral midline pruritis, ventral edema, stiffness, limb edema, fever, eyelid edema, colic, depression, and deaths were also observed in horses given the injectable product. Adverse reactions in a total of 11% of horses in one study. *Clostridial myostitis* occurred much less often.
    - CNS depression can occur in some horses following ivermectin ingestion.
- Dogs.
    - Acute anaphylactic reactions in dogs may result from microfilarial die off.
    - With genuine ivermectin toxicosis (most prevalent syndrome), dogs tend to show depression, ataxia, and sometimes coma, which may be prolonged or proceed to cause death. Some dogs show decreased menace response. Pupils will respond to light. Blindness commonly occurs and with time is reversible. Bradycardia and sinus arrhythmia reported.
- Chelonians.
    - Paresis, flaccid paralysis, may appear "dead".

Lesions

There are no characteristic lesions in ivermectin poisoned animals.

Diagnosis

- Clinical signs.
- Recent exposure to an avermectin. Remember that heartworm or *Onchocerca* die-offs can cause acute reactions, even when an appropriate dose is used.
- Analytical confirmation is **available** at the State Animal Disease Laboratory at Centralia, IL, USA. Desirable specimens include suspected source materials, serum, and liver. Contact the laboratory prior to sample submission. Telephone (618) 532-6701.

Treatment

- Activated charcoal and a saline cathartic are suggested if recently exposed by the oral route. Whether repeated doses of activated charcoal may prevent enterohepatic recycling of ivermectin is not known but it seems appropriate to try this approach until proven ineffective.
- If very recently given by the subcutaneous route and life-threatening toxicosis is anticipated, it may be possible to lessen the fraction absorbed by surgical excision (again no backup data is available).
- Symptomatic, supportive care. **Good nursing care**, most important.
- Atropine may correct bradycardia if present.
- Picrotoxin is a GABA antagonist and could, perhaps, be used to slowly titrate the animal toward normal. Excessive picrotoxin, however, will lead to seizures.
- Physostigmine (cholinesterase inhibitor). May have some benefit in comatose animal. Causes increased concentrations of acetylcholine at neurons. Will have very short beneficial effect. Physostigmine is recommended primarily when owners are inclined to elect euthanasia for ivermectin-poisoned animals. The short-term recovery that often follows physostigmine therapy may reassure the owner that recovery is likely. The drug is given very slowly (over 5 minutes) IV or IM at 1 mg/40 lb (0.06 mg/kg) in the dog.
- Epinephrine is indicated for acute anaphylactic reactions.
- A rapid onset of clinical signs (i.e., within 2 hours) may indicate a high level of exposure and a more guarded to poor prognosis, whereas a slower onset (i.e., after 6 hours) may indicate lower level exposure and a more favorable prognosis.
- Antihistamines are used if the old injectable **Eqvalen** product has caused histamine release and associated reactions.

Amitraz

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Dogs, horses, cattle	One hour to 2 days	1 - 3 days; may be lethal to swine, horses, young puppies	

Introduction

- A formamidine pesticide.
- Used as an acaricide and a tick repellant for dogs.

Sources

- Mitaban ® - An acaricidal dip concentrate for use and generalized demodecosis in dogs (19.9% amitraz). The preparation also includes xylene and propylene oxide.
- Tick-repellant collars such as Preventic ® (9% amitraz).
- Agricultural pesticides.

Toxicity

- The LD_{50} in rats is 800 mg/kg.
- In dogs, dermal absorption following dipping is a common route of exposure resulting in toxicosis. Ingestion by dogs of amitraz-containing collars is becoming more common as their use becomes more widespread.
- Amitraz is not approved for use in cats. Toxicosis has been reported in cats following administration of the liquid preparation in the external ear canal.
- Puppies up to 3 - 4 months old seem to be especially sensitive to amitraz.

Mechanism

- Centrally, amitraz exerts toxic effects by acting as an alpha-2 adrenergic agonist.
- These effects are reversible by yohimbine.

- α-2 adrenergic stimulation results in vasodilation, bradycardia, hypotension, coma, and decreased insulin release culminating in hyperglycemia.
- In addition, in the periphery both alpha-1 and alpha-2 receptors are stimulated. The effects at α-1 receptors sometimes result in hypertension.
- Amitraz also inhibits monoamine oxidase.
- Some of the clinical signs of Mitaban ® toxicosis are believed to be caused by xylene and propylene oxide.

Clinical Signs

- Dogs and cats-vomiting, sedation, depression, disorientation, ataxia, gastrointestinal hypomotility, bradycardia, hypotension, hypothermia, hyperglycemia, and seizures. Signs of CNS depression such as depression, ataxia, or coma may be due to coincidental xylene toxicosis. Clinical signs usually begin within hours of exposure. Bradycardia and hypotension appear to be due to the compound's central alpha-2 adrenergic effects and are reversible with yohimbine.
- A report of amitraz toxicosis in a group of horses lists observed signs as: tranquilization, depression, ataxia, and colic due to impaction.

Diagnosis

- History of exposure.
- Clinical signs.

Treatment

- Thoroughly wash with liquid dish detergent if dermal exposure has occurred.
- If a collar has been eaten, induce vomiting and/or remove collar via endoscopy. Administer activated charcoal.
- If solid or liquid preparations without xylene or other solvents have been ingested, give food mixed with activated charcoal then induce vomiting, if not contraindicated by bradycardia, hypotension, ataxia and/or weakness. Note, such problems are common after the onset of Amitraz toxicosis.
- Because hypotension may increase the severity of myocardial ischemia and thus arrhythmias, and because Amitraz may cause marked gut stasis and colic, atropine is contraindicated as a treatment for bradycardia.
- Ingestion of amitraz dip is unusual and is usually coincidental with toxicosis from dermal exposure. The presence of xylene in the formulation may make the wisdom of inducing vomiting or performing gastric lavage questionable. Give activated charcoal and bathe the animal with detergent.
- Yohimbine, 0.1 mg/kg IV antagonizes the alpha-2 adrenergic effects (bradycardia, hypotension, sedation, GI hypomotility), regardless of the route or amount of exposure. Repeat as needed.
- Fluids (IV) should be administered only to hypotensive animals and with care.
- Fluids may be contraindicated with marked bradycardia or hypertension.

Benzyl Alcohol and Benzoic Acid

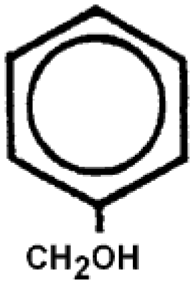
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Cats; neonates of all species	Hours to days with multiple doses	Up to a few days, potentially lethal	

Synonyms (of Benzyl Alcohol) - Benzene methanol, phenylcarbinol, CAS #100-51-6, phenmethylol

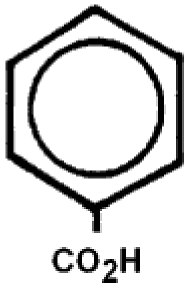
Sources

- Benzyl alcohol is sometimes added to "pyrogen-free" (rather than sterile) fluids for parenteral administration, e.g., 1.5% benzyl alcohol added to lactated Ringer's solution.
- Problems in human infants have occurred after quite low-grade exposure including the use of:
  - Sodium chloride USP with preservatives (0.9% benzyl alcohol).

  - Water for injection, bacteriostatic, USP (0.9% benzyl alcohol).
- Benzyl alcohol is clear and almost odorless.
- No longer as widely used as a preservative.
- Benzyl alcohol is available in toothache products as 1 - 2% solutions, mouthwashes, rinses, sprays as 0.05 - 10% solutions.
- Oil of jasmine contains 6% benzyl alcohol.
- Benzoic acid and benzoate salts are used as food preservatives, usually as a 0.1% concentration.
- **Note** - Each ml of Valium ® injectable contains 50 mg of sodium benzoate, 400 mg of propylene glycol, 100 mg of ethyl alcohol, 1.5 mg of benzyl alcohol and 5 mg of diazepam.
- Benzoic acid has been used topically as an antifungal agent and for the control of scabies in dogs.



Benzyl Alcohol
C_7H_8O



Benzoic Acid
$C_7H_6O_2$

Toxicity

- Cats and neonates of all species (such as calves, foals, etc.) are quite susceptible due to deficiency of glucuronyl transferase (poor glucuronide conjugation capacity).
- Toxicosis may occur after oral or parenteral exposure even to volumes of fluids used to correct only mild dehydration.
- Toxicosis reproduced in cats receiving 392 - 686 mg/kg in lactated Ringer's solutions.
- The LD_{50} of benzyl alcohol in dogs is 64 mg/kg.
- Lethal IV dose of benzyl alcohol in a 0.9% solution in dogs was 88 - 113 mg/kg.
- Toxicity from orally administered benzoic acid observed in children at 200 mg/kg/day.
- In humans, rectal administration of benzyl alcohol resulted in toxicosis.

Mechanism

- Benzyl alcohol is rapidly oxidized to benzoic acid. In most species benzoic acid is then conjugated with glycine to form hippuric acid or with glucuronic acid to form benzyl glucuronide. In the cat, more hippuric acid is probably formed. Hippuric acid is also toxic.
- Benzoic acid may accumulate which may contribute to a metabolic acidosis (well documented in neonatal humans) although additional (uncharacterized) mechanisms may also be involved. The acidosis is relatively resistant to bicarbonate administration.

Signs

- Feline:
  - Marked ataxia.
  - Slight to severe hyperesthesia, some animals respond violently to noise.
  - Fasciculations of the muscles of the head and ears.
  - Slight depression progressing to severe depression, inability to stand.
  - Pupils dilated and fixed.
  - Death.
  - Signs may progress to death within hours up to 1 1/2 days or longer depending upon dosage and frequency of administration.
- Foals and calves:
  - Decreased respiratory rate.
  - Gasping.

    - Erratic heart beat.
    - Death.
- Mice (Weanlings):
    - Decreased respiratory rate.
    - Gasping, mental confusion.
    - Ascending paralysis.
    - Subsequent, apparently painless death.
    - Adult mice exhibited no signs after the same doses.
- Classical Signs.
    - CNS depression.
    - Respiratory failure.
    - Vasodilation.
    - Hypotension.
    - Renal failure.
    - Convulsions.
    - Paralysis.
    - High oral exposures may cause gastroenteric irritation.
    - Ocular exposures can result in conjunctivitis, concentrated benzyl alcohol can cause corneal necrosis.
    - Anemia, thrombocytopenia, and leukopenia reported in benzyl alcohol-poisoned children. Benzyl alcohol administration may induce hemolysis.

Lesions

- Gross postmortem lesions generally absent.
- Intracranial hemorrhages sometimes observed in poisoned children.

Treatment

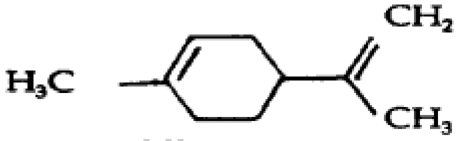
- Correct acidosis with bicarbonate (1 - 3 mEq/kg) in fluids (**not containing benzyl alcohol**).
- Bicarbonate may (perhaps) also promote excretion.
- Fluids to promote excretion.
- Artificial respiration.
- Control seizures with phenobarbital or if necessary pentobarbital.
- Irrigate eyes if ocular exposure has occurred.

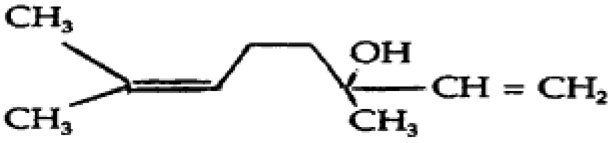
Citrus Oil Extracts

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Cats, dogs	Minutes to hours	Hours to 1 day; unlikely to be lethal	

Sources

- Crude citrus oil extracts have been formulated into preparations labelled for use on pets, "to control itching due to" (in tiny letters), "fleas, ticks, and lice", (in giant letters). This was an attempt to avoid EPA safety testing by avoidance of an insecticidal claim on the label.
- These should not be confused with formulations containing purified d-limonene another citrus derived agent.
- d-limonene has also been used as a wetting and dispersing agent, as a food flavor, and as a fragrance in various detergents.
- A third citrus derivative, linalool, is now on the market alone (in dip solutions) and in a spray product in combination with d-limonene and the mixed function oxidase inhibitor, piperonyl butoxide.


d-limonene


Linalool

Mechanism of Action

- The mechanism of action of these agents is not thoroughly understood.
- There is evidence of both centrally and peripherally acting vasodilation. Prolonged vascular effects of linalool appear to be related to a nervous system mechanism of action.

Absorption, Distribution, Metabolism and Excretion (ADME)

- When applied topically, at least some of the compound(s) is (are) absorbed through the skin which probably accounts for some of the systemic effects. With regard to the absorbed fraction of linalool, a major portion is conjugated in the liver to form a glucuronide or sulfate conjugate with significant excretion in the urine (a total of 55% of administered radiolabel from linalool is excreted in the urine in one form or another). Some linalool undergoes enterohepatic recycling.
- Orally administered linalool is rapidly absorbed.
- Approximately 25% of orally administered linalool is eliminated by metabolism to CO_2.

Toxicity

- Rat oral LD_{50} = 2790 mg/kg.
- Toxicosis resulting from citrus oil extracts is most likely in cats - Cats died at the recommended concentrations of the preparation containing crude citrus oil.
- Cats are, however, highly tolerant of d-limonene. For example, cats treated with 15 times the recommended concentration in the final dip solution survived with no supportive or detoxification treatment. The cats treated at this level did, however, display marked, although temporary signs of toxicosis. In addition, 2 cats similarly tolerated exposure to 16 times the recommended concentration as did one cat treated at 20 times the recommended rate.
- The tolerance of cats to a spray product containing a combination of d-limonene, linalool, and piperonyl butoxide is less, with 10 times and higher applications producing serious clinical signs. At 20 times the recommended concentration of the 3 active ingredients, the product was potentially lethal. The type of formulation, however, as an already diluted solution for spraying on the animal, would reduce the chance for excessive application to the animal.

Signs

- Cats treated with excessive amounts of citrus-based insecticides tend to display ataxia, central nervous system depression (or generalized paralysis), and at least in the case of d-limonene, profound hypothermia when exposed to high rates of exposure.
- Cats exposed to crude citrus oil products may die after a period of central nervous system depression.
- Cats given excessive exposure to the spray containing linalool, d-limonene and piperonyl butoxide were recumbent for up to 6 days after topical application.
- With topical exposure to d-limonene alone, recovery in healthy cats should be expected within 6 - 12 hours.

Lesions

The only lesion likely to be observed in excessively treated cats is scrotal and associated (self-trauma-induced) perineal dermatitis in male cats.

Treatment

- Bathing in a liquid dish detergent solution is recommended to remove any significant residual insecticide.
- Keep the animal warm but well ventilated.

- Other therapy is symptomatic and supportive.
- Atropine is **not** indicated.

Note

Do not ignore the possibility of other more toxic agents being used on or around the cat and causing the toxic syndrome (i.e., other insecticides or various other toxicants used in the home or on the animal).

Stipa robusta - Sleepy Grass

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Central Nervous System Depression
Horses	Days	Up to 2 days; unlikely to be lethal	

Description

Stout (5/16-inch wide leaves), perennial grass forming erect clumps, 2 - 4 feet tall. Several branches at each node, narrow spikelets about 1/2 inch long tipped by a long, dry, twisted, 1-inch-long awn.

Habitat

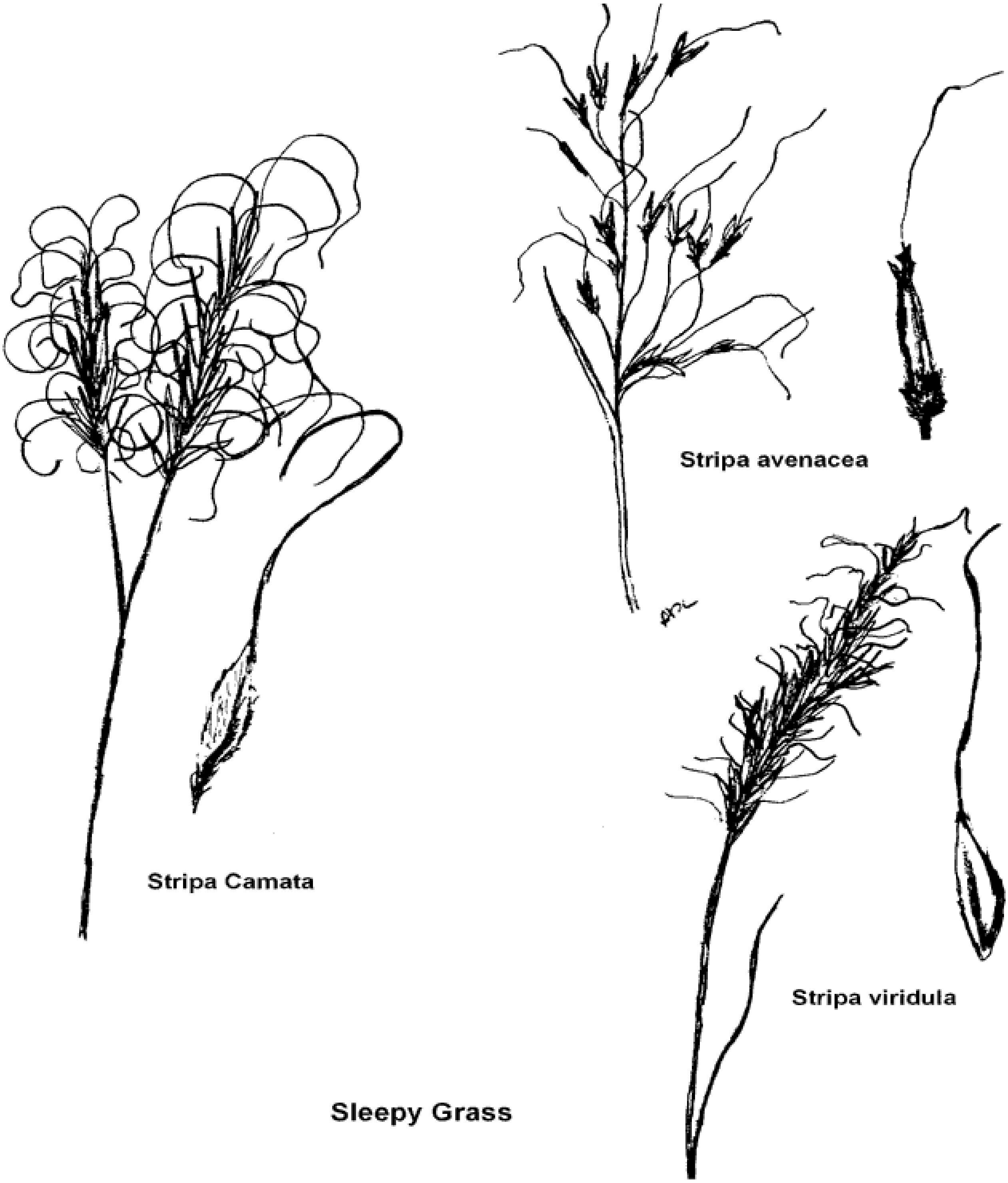
Toxicoses reportedly have occurred in the Sacramento and Sierra Blanca Mountains of New Mexico.

Susceptible Species

Poisoning occurs in horses; cattle are resistant.

Signs

- Varying degrees of CNS depression. May be severe enough to cause somnolence, sternal or lateral recumbancy.
- Once poisoned, horses may avoid thereafter.



Stripa avenacea

Stripa Camata

Stripa viridula

Sleepy Grass

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Central Nervous System Depression
Piperazine	Cats, dogs	Within 24 hours	1 - 3 days; rarely lethal	
Bendodiazepines (e.g. diazepam)	Dogs, cats	1 - 4 hours	Hours to 3 days; rarely lethal in dogs, potentially lethal hepatoxicity in cats	

			(after 1 week of administration)
Barbiturates Ingestion by carnivores and scavengers [e.g. dogs, foxes, coyotes, raptors, etc.] of pentobarbital or other euthanasia drugs in recently euthanatized animals (generally livestock) can result in severe, potentially lethal (esp. in raptors) toxicosis	All species	Minutes to hours	Hours to a few days; potentially lethal
Tranquilizers	All species	Minutes	Hours potentially lethal after intra-arterial injection
Phenothiazine tranquilizers	All animals	Minutes to hours	Hours to 2 days; infrequently lethal
Isopropanol	Cats, dogs	Minutes	Hours to 1 day; potentially lethal
Ethanol Ethanol toxicosis occurs occasionally in cage birds, dogs, an cats from alcoholic beverages, dogs that ingest bread dough (causes ethanol toxicosis and/or severe digestivetract distention due to "rising" of the dough *in vivo*), silage-feed or stillage-fed cattle (also brewer's grains), and cedar waxwings that gorge on fruits that have fermented alcohol late in the season.	All species	Minutes	Up to 3 days
Methylene chloride and other hydrocarbon solvents	All species	Minutes to hours	Hours to 3 days; lethality varies among compounds

- Piperazine (same mechanism as ivermectin)
- Benzodiazepines
- Phenothiazine in Small Animals (See Toxicants that Affect the Skin)
- Tranquilizers
- Barbiturates (Ingestion by carnivores [e.g., dogs, other mammalians, carnivores, raptors] of pentobarbital in recently euthanatized animals can result in severe, potentially lethal [especially in raptors] toxicosis)
- Ethylene Glycol (See Toxicants that Cause Acidosis)
- Ethanol (Occasionally in cage birds from alcoholic beverages; reported in silage-fed cattle; in small animals that ingest bread dough; and in birds that eat fermented fruits [e.g., cedar waxwings])
- Isopropanol
- Methylene Chloride and Numerous Other Hydrocarbon Solvents (See Toxicants that Affect the Respiratory System)
- Domoic acid (cause of amnesic shellfish poisoning) (Rigid analog of neurotransmitter glutamate. Domoic acid activates Fos, which is correlated with neurologic damage. (See Peng YG, Ramsdell JS. Brain Fos induction is a sensitive biomarker for the lowest observed neuroexcitatory effects of domoic acid. Fundam Appl Toxicol 1996; 31:162-168. - PubMed -)
- Yet-to-be-identified amnesic toxin in *Pfiesteria piscida* a photosynthetic, polymorphic protozoan that also causes dermonecrosis in riverine and coastal fish.

Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)

V. Beasley

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1. Toxicants that Act as Cholinergic Blockers

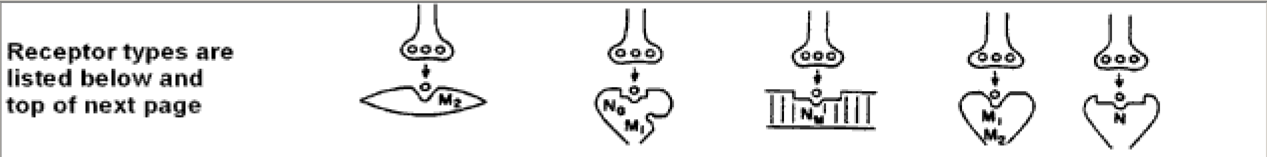
Background

Acetylcholine is the neurotransmitter of cholinergic neurons in the autonomic and central nervous systems.

Anticholinergic-Synonyms

- Cholinergic blockers.
- Antimuscarinic.
- Antiparasympathetic.
- Cholinolytic.
- Parasympatholytic.
- Antispasmodic.
- Spasmolytic.
- Cholinergic neurons:
    - Include all sympathetic and parasympathetic preganglionic neurons and nerve supply to the adrenal medulla.
    - Parasympathetic postganglionic neurons (autonomic effector sites).
    - Sympathetic postganglionic neurons which innervate sweat glands.
    - Sympathetic postganglionic neurons which innervate blood vessels in skeletal muscle and produce vasodilation when stimulated.

Types of postsynaptic Cholinergic Receptors

	Postganglionic Parasympathetic	**Preganglionic Autonomic**	**Somatic Motor**	**CNS**	
 Receptor types are listed below and top of next page M2 NG M1 NM M1 M2 N					
Cholinoceptive Site	**Autonomic Effector Cell**	**Autonomic Ganglion Cell**	**Striated Muscle**	**Central Neurons**	
Cholinomimetic Agent	Muscarine	DMPP(N_G) McN-A-343(M_1)	PTMA	Muscarine, Oxotremorine	Carbachol
Cholinergic Blocking Agent	Atropine	d-TC	d-TC	Atropine	d-TC

Receptors

- There are three (3) categories of cholinergic receptors: muscarinic, nicotinic, and CNS.

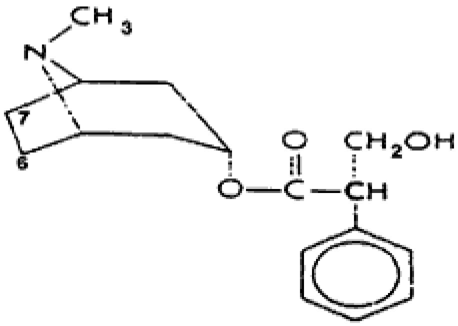
7. Muscarinic receptors (M_1, M_2):
    - Smooth muscle.

   - Cardiac muscle.
   - Exocrine glands.
   - CNS.
   - Transmitting agents.
      - Acetylcholine in normal concentrations.
      - Muscarine.
   - Non-depolarizing blocking agents include:
      - Atropine and other belladonna alkaloids.
8. Nicotinic receptors (N):
   - Autonomic ganglia.
   - Skeletal muscle (Nm).
   - CNS.
   - Transmitting agents.
      - Acetylcholine in normal concentrations.
      - Nicotine in low concentrations.
   - Blocking agents.
      - Nicotine in high concentrations produces a depolarizing blockade of ganglia and skeletal muscle.
      - Acetylcholine also causes a depolarizing blockade at very high concentrations as occurs with serious toxicosis due to cholinesterase inhibitors, i.e., organophosphorus or carbamate insecticides.
      - Curare - Causes a non-depolarizing blockade at skeletal muscle (neuromuscular receptors). Active agent = d-tubocurarine = d-TC.
      - Nicotinic sites are not highly sensitive to atropine.
9. Central nervous system receptors (M_1, M_2, N, possibly others).

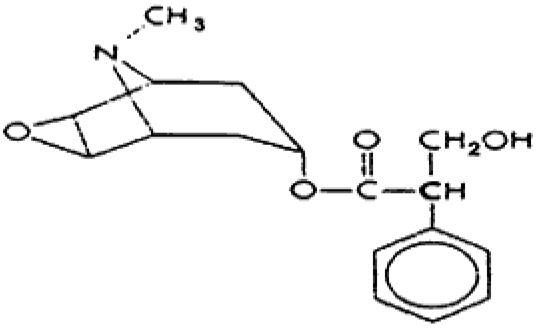
Nondepolarizing Blockers at Muscarinic (Cholinergic) Receptors

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Atropine (D, L hyoscyamine)	Cattle, dogs, cats, and esp. horses	Minutes	Hours to a day in small animals, horses (up to 3 days); up to several days in cattle; potentially lethal, esp. in horses	
Scopolamine (L-hyoscine)	Effects similar to atropine; toxicosis unlikely when used at recommended doses			
Benztropine (Cogentine ®)	Effects similar to atropine; toxicosis unlikely when used at recommended doses			
Aminopentamide (Centrine ®)	Effects similar to atropine; toxicosis unlikely when used at recommended doses			
Atropine methyl nitrate	Toxicosis unlikely when used at recommended doses			
Scopolamine methyl bromide	Toxicosis unlikely when used at recommended doses			
Homatropine methyl bromide	Toxicosis unlikely when used at recommended doses			
Propantheline (Pro-Banthine ®)	Toxicosis unlikely when used at recommended doses			
Glycopyrrolate (Robinul-V ®)	Toxicosis unlikely when used at recommended doses			

Atropine, Scopolamine and Others



Atropine



Scopolamine

Introduction

- Parasympatholytic agents prevent acetylcholine (Ach) from producing its effects at muscarinic receptors in the brain and at postganglionic receptors.
- Inhibit effects of Ach on Ach responsive nerves, smooth muscle cells, and glands, i.e., innervated by sympathetic postganglionic cholinergic fibers (muscarinic receptors).

Sources

- Various drugs in some antispasmodics, antihistamines, antipsychotics, antidepressants, and some over-the-counter sleep preparations act as non-depolarizing blockers of muscarinic receptors.
- Scopalamine ophthalmic solution 0.25% and atropine ophthalmic solution (up to 4%).

Atropine (DL-Hyoscyamine)

- A natural tropane alkaloid extracted from the belladonna plant (*Atropa belladonna*), a nightshade shrub. Principle alkaloid in jimson weed (*Datura stramonium*).
- Tincture and extract of belladonna may still be encountered in homes.
- Atropine is a tertiary amine - not charged (penetrates blood-brain barrier).
- Atropine methyl nitrate is charged (little penetration of BBB).
- Belladonna alkaloids are rapidly absorbed from mucous membranes.

Scopalamine (L-Hyoscine) (Epoxidized Hyoscyamine)

- Occurs in the *Henbane* plant (*Hyoscyamus niger*) and in jimson weed (also called Jamestownweed) (*Datura stramonium*) and a derivative, stramonium powder.
- The L-isomers are more potent both in peripheral and central nervous systems.

Classes of Drugs

- Tertiary amines-no charge-penetrate CNS, e.g. atropine, scopalamine.
  - Benztropine (Cogentine) used in treatment of Parkinsonism.
  - Opthalmics.
- Quaternary analogs-charged, therefore do not tend to enter CNS.
  - Atropine methyl nitrate.
  - Scopalamine methylbromide.
  - Homatropine methylbromide.
  - Propantheline (Pro-Banthine).
- Certain antihistamines, antidepressants, and antipsychotics also have cholinergic blocking properties.

Mechanism

Atropine does not affect acetylcholine release. However, atropine and all of the parasympatholytic drugs act as competitive antagonists at acetylcholine receptors where acetylcholine exerts a parasympathomimetic or muscarinic effect. Also, the effects of acetylcholine receptors beyond parasympathetic postganglionic endings are blocked. However, following atropine administration, acetylcholine still exerts its sympathomimetic and nicotinic effects, including acting at voluntary muscle receptors.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Variable oral absorption, normally prolonged in toxic doses due to decreased GI motility.
- Metabolized in liver to tropic acid, tropine and esters of tropic acid and has glucoronide conjugates formed.
- Elimination half-life (man) 2 - 3 hours, longer in children.

Toxicity

Low doses of atropine (0.044 mg/kg) decreased GI motility for 8 - 12 hours in horses.

Signs

- Produces both peripheral and CNS symptomatology.
- Blocks vagus-rapid heart rate at high enough doses (low doses may stimulate vagal medullary centers causing bradycardia). Ventricular arrhythmias and EKG changes (widened QRS, prolonged QT interval) may occur.
- Urinary retention, constipation.
- Dry mouth.
- Decreased gastrointestinal motility, occasionally vomiting. **Colic in horses**.
- Some mild CNS depression can occur, CNS stimulation may precede depression. Behavioral changes may occur, e.g., "disorientation", hallucinogenic in man.
- Mydriasis, pupils may be unreactive to light.
- Loss of accommodation (cycloplegia)-cannot see well up close, distant vision remains sharp.
- Hyperthermia, hypertension, ataxia, dysphagia.
- Very high doses, coma and skeletal muscle paralysis may occur.
- Drop of urine obtained from an atropine-poisoned animal may cause mydriasis if placed into another animal's eye. Occasionally used as a diagnostic aid.

Treatment of Poisoning

- Activated charcoal, saline cathartic-for recent oral exposure.
- Do not use phenothiazine tranquilizers.
- For severely poisoned:
  - **Very** slow IV-physostigmine to the point at which delirium and coma are abolished or SQ (*see below*).
- Monitor EKG-in general sinus tachyarrhythmias, do not need to be treated (slowed) unless signs of cardiac insufficiency develop. Tachyarrhythmias unresponsive to physostigmine may respond to propranolol administered at 0.2 mg/kg (dog dose) IV, slowly.
- Physostigmine.
  - Indications in treatment of atropine or other cholinergic blocker overdose:
    - Diagnostic tool.
      - If administered slowly IV over 5 minutes and if get recovery, the diagnosis is confirmed. Begin with 0.5 mg total dose (based on human pediatric doses), may need to be repeated.
      - Animal could fail to recover if:
        - Previously anoxic: may already have brain damage.
        - If ingested a combination medication.
    - Life threatening toxicoses-as a treatment, i.e., for atropine poisoned animals which display a notable amount of:
      - Convulsions.

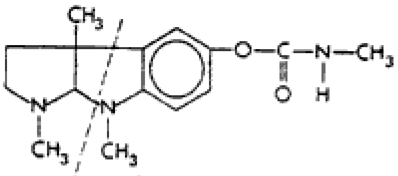
    - Hypertension.
    - Arrhythmias: use with caution, physostigmine can cause asystole.
  - Do not give repeatedly just to keep awake. The lowest total effective dose should be administered, no more often than every hour.
  - Dosage
    - A pediatric therapeutic trial dose is 0.02 mg/kg slow (over 5 minutes) IV.
    - Recommended at 0.055 mg/kg (1 mg/18 kg) for dogs slow (over 5 minutes) IV.
    - Recommended for horses at 0.1 - 0.6 mg/kg IM or slow (over 5 minutes) IV.

Note

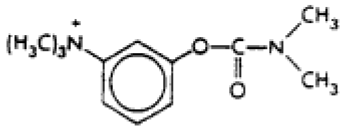
- Physostigmine :
  = a naturally occurring carbamate alkaloid
  = eserine
  = obtained from Calabar bean = ordeal bean
- Physostigmine is hydrolyzed by cholinesterase but much slower than acetylcholine.
  - Physostigmine therefore competitively inhibits cholinesterase and less acetylcholine is degraded.
  - Results in elevated concentrations of acetylcholine which compete with atropine for the cholinergic receptor (nicotinic, muscarinic, or gland).

  Physostigmine is **not charged** so that it penetrates the CNS.

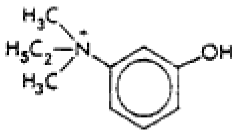
- Charged analogs - such as neostigmine (Prostigmine); pyridostigmine (Mestinon), benzpyrinium (Stigmonene), and decamarium (Humorsol) are quaternary ammonium analogs which do not efficiently penetrate the BBB. Since the primary lethal effects of atropine toxicosis are central, these are not used in treatment of atropine toxicosis.



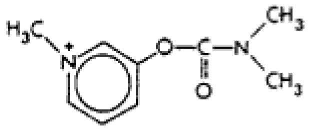
Physostigmine



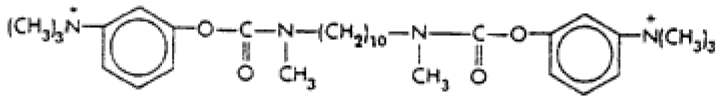
Neostigmine



Edrophonium



Pyridostigmine



Demecarium

Atropa belladonna - Belladonna Plant

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Cattle, horses, and esp. swine	Minutes to hours	Hours to 3 days, poisoning is rare	

Synonyms - Deadly nightshade (a Solanaceae member), nightshade, sleeping nightshade

Description

A. belladonna is a coarse herb with a thick root, and with highly branched stems which grow from 0.6 - 1.6 m tall. The leaves are large (approximately 15 cm [6 inches] long), ovate, and alternately inserted but develop so rapidly that they may appear to be inserted in pairs at the same point with one member of each pair larger than the other. Flowers are solitary, almost 2.5 cm long, 5 parted, with a 5-pointed calyx, a tubular corolla, and dull purple. Single berries (1 - 1.3 cm in diameter) are purple to black when ripe. Reddish sap.

Habitat

Native to Europe, a garden plant in the USA - Occasionally encountered, rarely escapes from gardens but forms no extensive growths.

Toxicity

- Atropine, which is present throughout the plant, increasing to maximum at maturity.
- Ingestion of as few as 3 berries was fatal to a child.

Signs

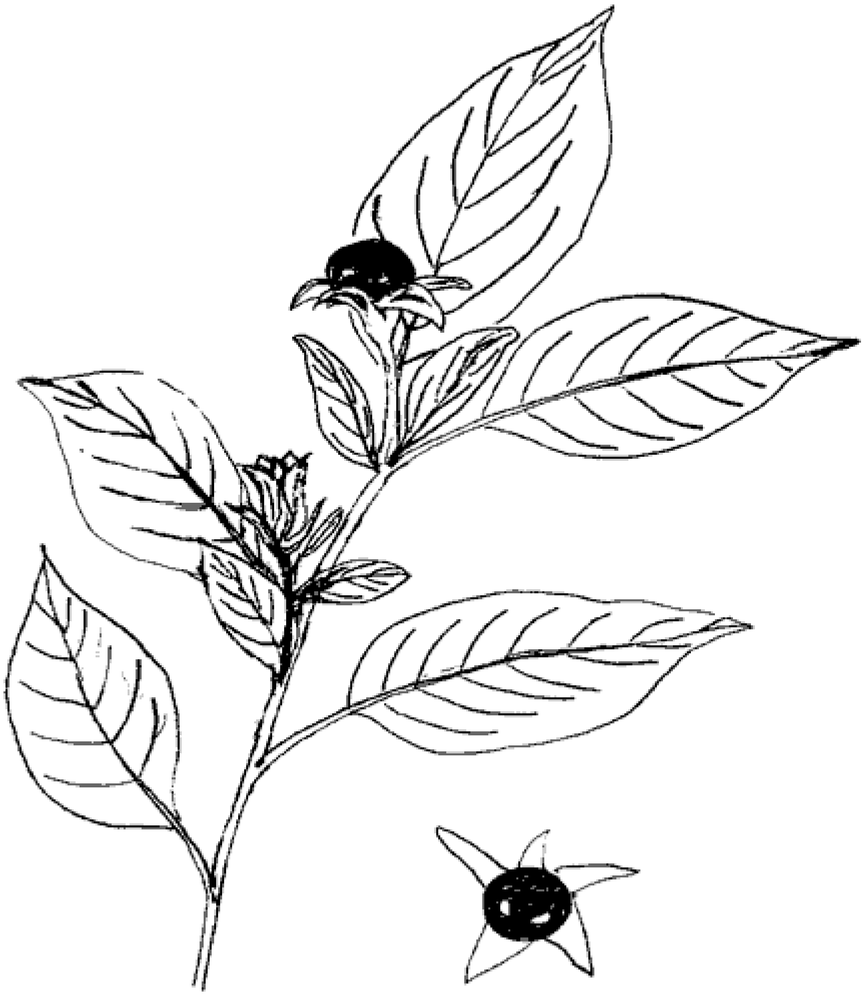
Poisoning is rare. Trembling, excitement, followed by prostration in about 10 hours. Tachycardia, weak pulse, extreme mydriasis, difficulty in short range vision (accommodation), dyspnea, gastric and/or intestinal atony, coma, hyperthermia (in humans and perhaps in animals that sweat), death.

Diagnosis

Evidence of consumption, presence of atropine effects, placing a drop of urine into a cat's eye causes mydraisis.

Treatment

As for atropine ingestion (see Introduction to Anticholinergic Agents section).



Deadly Nightshade - *Atropa belladonna*

Henbane (*Hyoscyamus niger*)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Poultry, cattle, sheep	Minutes to hours	Hours to 3 days	

Synonyms

- Black henbane, henbane, stinking nightshade, poison tobacco, fetid nightshade, and insane root.
- Another member of the Solanaceae.

Description

An annual or biennial, coarse, hairy, erect herb, 1 - 4 feet tall with coarsely toothed, oblong leaves 3 - 8 inches in length. Flowers are single on short pedicels or in the leaf angles becoming crowded near the tips. Flowers are 5 lobed with greenish-yellow or yellowish-white with a purple throat and veins. Fruits are enclosed in a 5 lobed capsule. Spindle-shaped roots.

Habitat

- In the USA, primarily found in the northeastern states.
- Scattered in southern Canada, northern USA, locally common in some areas of the northern Rocky Mountain states.
- Usually in dry soils, in roadsides, other "waste areas".

Toxicity

- Atropine and scopalamine.
- The seed is poisonous.

Susceptible Species

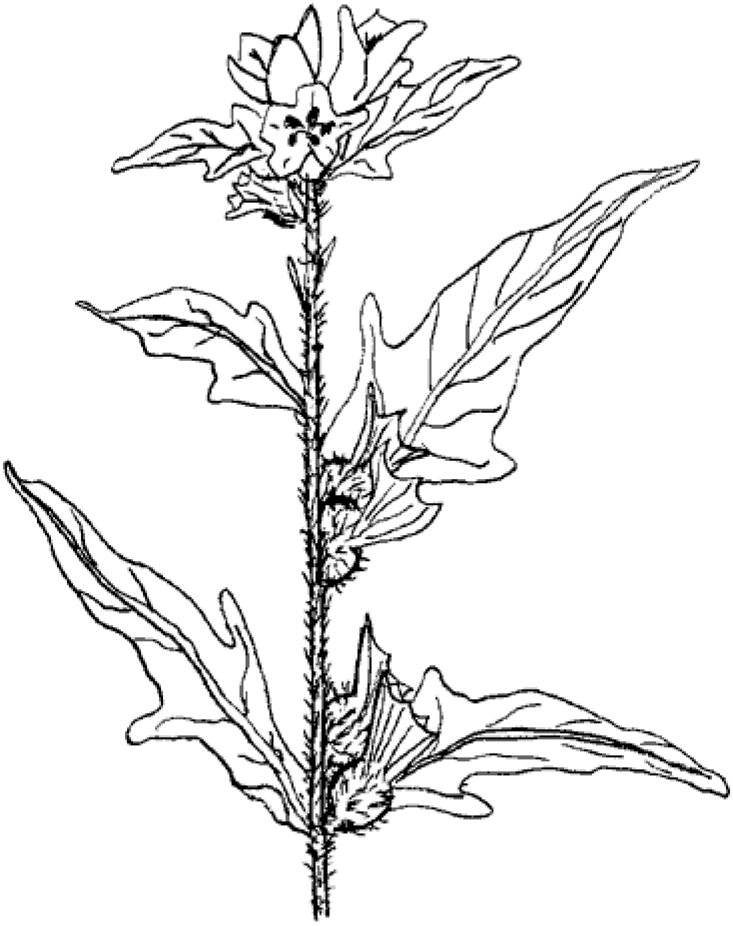
- Has poisoned livestock, children.
- Fowl were poisoned from eating seed.

Signs

- Similar to other anticholinergic poisoning.
- Poisoning is rare, perhaps because the plant is distasteful.

Treatment

- As for atropine ingestion (see Introduction to Anticholinergic Agents section).



Hyosycamus niger

Datura stramonium - Jimson Weed

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Horses, cattle, sheep, swine, chickens, ostriches	Minutes to hours	Hours to 3 days	

Synonyms

- Jamestown weed, thornapple, devil's trumpet, mad apple, and stink weed.
- Solanaceae member.

Description

- Plant is a stout, coarse, annual herb which is 0.6 - 1.6 m tall with spreading branches and simple alternate leaves (15 - 20 cm [6 - 8"] long) which are coarsely and irregularly toothed with a rank odor.
- Flowers are large, white or purple and tubular; 5 - 10 cm (2 - 4") long.
- Fruit is a spiny capsule 2.5 - 5 cm (1 - 2") in diameter which can be split into four parts. Sheds small brown to black seeds; seeds contaminate corn, etc.

Habitat

- Fertile soils where other plants are scarce - e.g. barnyards, fertile cultivated fields, hog lots.
- Midwest as far north as southern Minnesota, Wisconsin, Michigan.

Toxic Principle

- Tropane alkaloids:
  - Hyoscyamine = an isomer of atropine.
  - Scopalamine = L-hyoscine = epoxidized hyoscyamine.

Toxicity

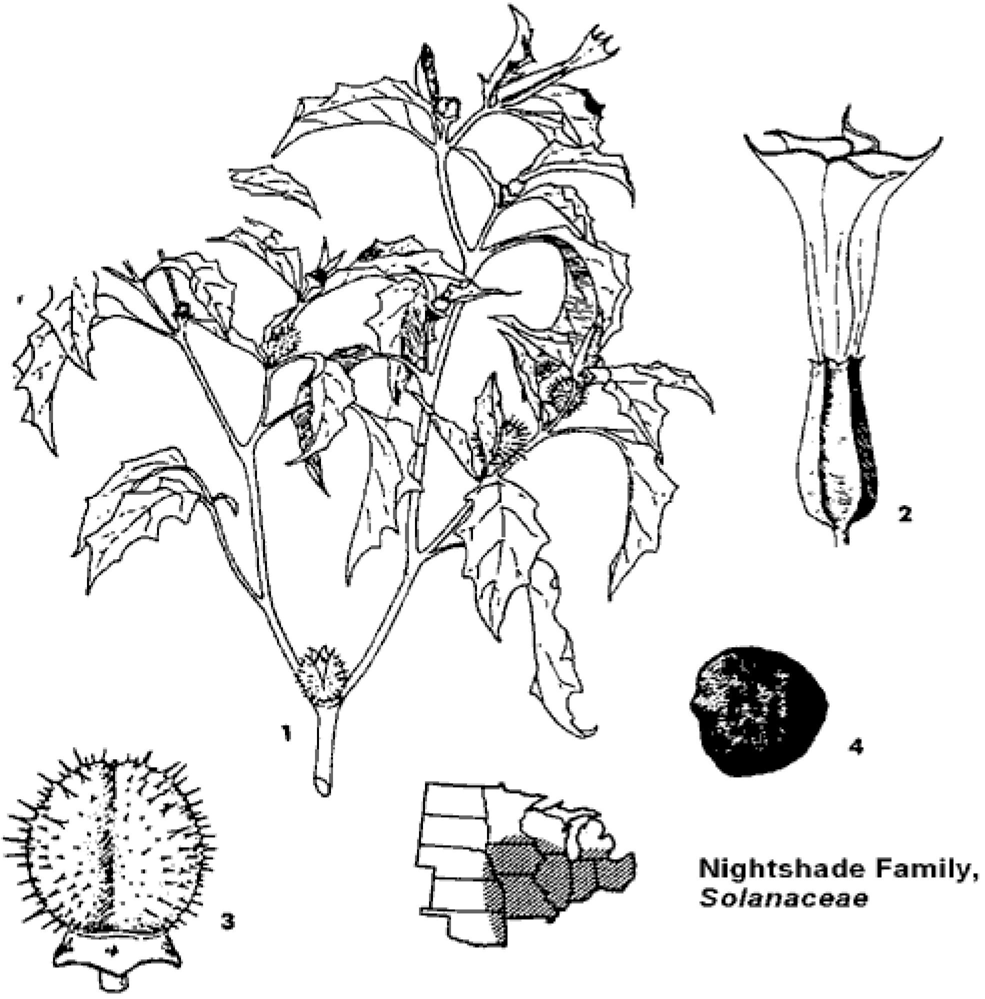
- Poisoning is infrequent; regarded as unpalatable.
- Poisoning occurs primarily when hungry animals are turned into an area where better forage is absent.
- Poisoning may also result when a large amount is present in hay.
- Palatability may increase when sprayed with 2,4-D or similar herbicides.
- Possible poisoning as a result of seeds in grains and feeds (seeds contain 0.05% alkaloid by weight).
- Entire plant is toxic, seeds most often implicated.
- Pigs appear to be very sensitive to seeds, 2.2 - 2.7 mg/kg/day reported to cause toxic signs.
- Toxic signs seen in cattle given seeds at 0.06 - 0.09% bw/day.

Signs

- Hypothermia in animals, hyperthermia in man. Death from respiratory paralysis.
- Depression, anorexia, weight loss, tachypnea, tachycardia, mydriasis, polyuria, polydipsia, diarrhea.
- In cattle see excitability, tremors, rumen atony, nervousness, bloat, tenesmus, and anorexia. Death occasionally reported.
- In goats, *Datura stramonium* ingestion was accompanied by tachypnea, tremors, drowsiness, recumbency, and altered locomotion.
- In sheep, *Datura stramonium* ingestion was associated with ataxia, inability to stand, tachypnea, reduced drinking and mild tremors.

Treatment

Similar to atropine ingestion (see Introduction to Anticholinergic Agents section).



Jimsonweed, *Datura stramonium* - L. **1**, upper portion of plant; **2**, flower; **3**, seed pod; **4**, seed. **Annual**, reproducing by seed. **Roots** thick, shallow, extensively branched. **Stems** smooth, thick, erect, branching widely in upper part, 2 to 4 feet (0.6 to 1.2 m) tall. **Leaves** alternate, large, course, smooth, ovate, with irregularly toothed edges and a distinctive rank odor. **Flowers** large, funnel-shaped, white to pinkish, 2 to 5 inches (5 to 12.5 cm) long, borne singly on short stalks in the axils of the branches. **Seed pod** about 1 inch (2.5 cm) in diameter, egg-shaped, covered with short, sharp spines. **Seed** dark brown to black, kidney-shaped, flattened, surface irregular and pitted. **Found** in cultivated crops on rich land and especially in old feedlots. This plant contains poisonous materials.

Anticholinergic Mushrooms

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Mostly small animals	Minutes to hours	Hours, rarely lethal	

Species

Amanita citrina, Amanita cokeri (solitaria), Amanita crenulata, Amanita muscaria, Amanita pantherina, intergrade species of *Amanita pantherina, Amanita cothurnata,* and *Amanita gemmata*. Possibly *Panaeolus campanuiatus* and *Panaeolus* species.

Description

- *Amanita* sp. - large and colorful.
  - Ring around stem - "ring of death".
  - Cup on bottom of stem - "cup of death".

Toxic Principle

- Thermostable toxins--not removed by boiling. Not destroyed by drying.
- Contains isoxazoles (ibotenic acid, muscazone, and muscimol) cause most clinical signs. Pantherin, stizolobic acid, stizolobinic acid (L-dopa oxidation products) or tricholomic acid are also present. All of these have largely anticholinergic effects in the peripheral nervous system.
- Despite previous reports, there is no evidence that these mushrooms contain atropine (pilzatropine), hyoscyamine or stramonium.
- The isoxazole compounds apparently inhibit the effects of GABA which contributes to CNS dysfunction. The anticholinergic effects may sometimes be less appreciable.
- Occasionally small amounts of muscarine occur causing cholinergic effects, but usually these are clinically insignificant. Neverthless, in some localities and some years the cholinergic symptoms predominate.

Toxicity

Fatality rate probably less than 1%, but reports are still inadequate. With appropriate treatment, an adult male human survived eating 20 large *Amanita muscaria*.

Signs

- Poisonings in small animals are rarely diagnosed.
- The anti-cholinergic syndrome includes both central and peripheral signs.
- The cholinergic effects of muscarine (when they occur) are mostly peripheral.
- Humans - onset within 30 - 60 minutes. Usually a feeling of drowsiness is quickly followed by a state of confusion resembling alcoholic intoxication. Dizziness, ataxia and euphoria may progress into hyperkinetic activity, muscle cramps and spasms, and even delirium. Visual disturbances and even hallucinations may occur, vomiting usually does not take place. Drowsiness to deep sleep or even coma terminate the episode which usually lasts for about four hours.

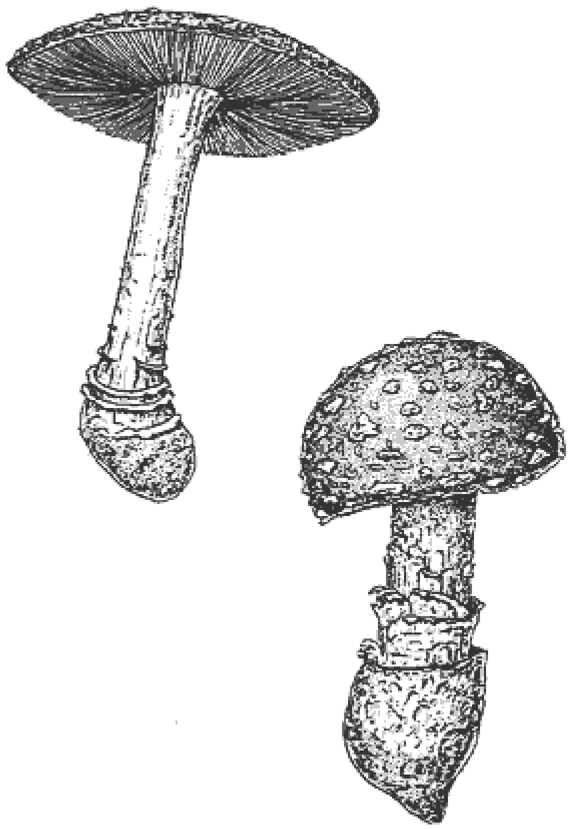
Diagnosis

Muscimol has been detected in the urine and, if analysis is available, may be used for confirmation of this type of ingestion.

Treatment

- Unless contraindications exist, emesis should be initiated. If contraindications are present, endotrachael intubation should precede gastric lavage. Lavage should be done with a large gastric tube. Activated charcoal and a saline cathartic should be administered after emesis (if not contraindicated) or lavage. Rapid action to prevent absorption is particularly important with this group of mushrooms since the latent period is so short. Spontaneous vomiting rarely occurs.
- Enhancement of excretion via forced diuresis is suggested with oral and IV fluids, and osmotic diuretics or furosemide.
- Treatment with physostigmine (as for atropine ingestion in Introduction to Anticholinergic Agents section) should be considered only if the anticholinergic effects (tachycardia, dilated pupil, hallucinations, decreased bowel sounds, dry mouth, etc.) are **severe**.
- Treat in response to, not in anticipation of clinical signs; they are variable.

- Atropine: **only** if cholinergic signs, e.g., severe bradycardia, is present.

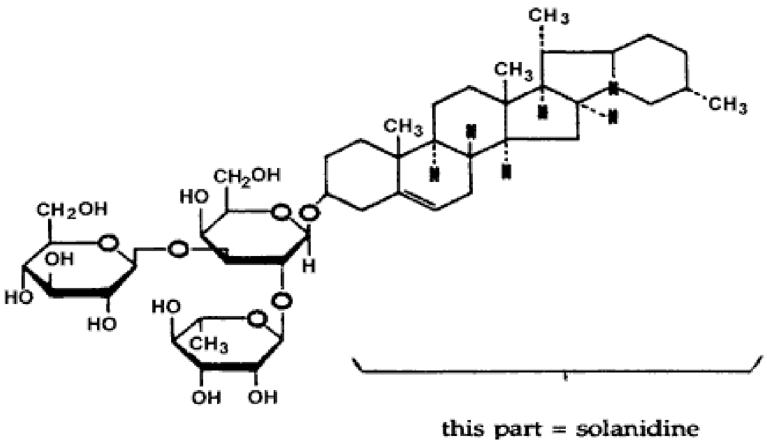


Amanita muscaria - Wide red to yellow cap, white gills, and whitish stalk with wavy "skirt" and bulbous base are characteristic of this mushroom.

Introduction to Solanaceae, Solanine, Solanidine, Solanocapsine, as well as Atropine and Atropine-Like Toxins in the Solanaceae

Solanine

Solanine is a glycoalkaloid (sugar attached to an alkaloid). Because of the structure of the alkaloid portion of the molecule, solanine also is referred to as a steroidal alkaloid. The aglycone (sometimes called an alkamine aglycone) is called **solanidine**. The word aglycone simply means the compound remaining after the sugar moiety has been removed.



Overall Structure = Solanine

Sources

Solanaceae family.

Toxicity

- Glycoside (solanine) more toxic than aglycone (solanidine).
- Rapid fecal and urinary excretion.
- Toxic dose of solanine given orally to sheep was 225 mg/kg.
- See individual plants in pages that follow.

Absorption, Distribution, Metabolism and Excretion (ADME)

Solanine is poorly absorbed from GI tract.

Mechanisms of Action and Clinical Signs

- Principle effects of solanine alkaloid poisoning are gastrointestinal tract irritation and CNS impairment.
- Reportedly inhibits cholinesterase activity.
- Reportedly has weak cardiotonic activity.
- Depression, recumbency occurs in horses, cattle, swine.
- Exanthematous form-ulcerative stomatitis, conjunctivitis, diarrhea, and eczema of legs in cattle and pigs.

Signs

- The signs of poisoning due to solanine and atropine are somewhat parallel in that both may produce pupillary dilation, ataxia, muscular weakness, restless or thrashing movements, and body temperature elevation (the latter may occur with atropine toxicosis in animal species that sweat; not documented in animals; but occurs in atropine-poisoned humans).
- They differ in that solanine often produces gastroenteritis, depression, salivation, sweating in capable species and dyspnea. In man, headache is common, and stupefaction and loss of sensation have been reported.

Lesions

- Gastroenteritis.
- Congestion of cerebral membranes and kidneys.

Atropine, Structurally and Toxicologically Related Compounds and Solanocapsine

Some members of the Solanaceae have primarily solanine-type alkaloids (solanine, solanidine, etc.); others have atropine or atropine-like compounds; and still others may have both solanine-type as well as atropine-like constituents which complicate therapeutic considerations. Jerusalem cherry (*Solanum pseudocapsicum*), black nightshade (S. nigrum and other species), jessamine (*Cestrum* spp.) ground cherry (*Physalis* spp.), and tomato leaves and unripe fruit (*Lysopersicon*) often contain both solanaceous and atropine-like alkaloids and clinical signs from either may predominate. Potato (S. *tuberosum*) may also contain both types of alkaloid; however, the atropine-like constituents tend to predominate. In addition to the alkaloids mentioned above, Jerusalem cherry (S. *pseudocapsicum*) also contains solanocapsine, which produces marked bradycardia. These considerations are alluded to in the following sections.

Physalis spp. - Ground Cherry (Members of the Solanaceae)

Physalis heterophylla - Ground cherry, husk-tomato.
P. subglabrata - Ground cherry, husk-tomato.

Several other *Physalis* plants. Other trivial names for various *Physalis* spp. include Chinese or Japanese lantern plant, gooseberry tomato, strawberry tomato, winter cherry, and yellow henbane.

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
All species	Minutes to hours	Hours to 3 days	

Description

- There are a large number of *Physalis* spp. cultivated in the United States for their attractive Chinese lantern-like fruits.
- *P. heterophylla*.
    - Erect, perennial herb, with branched or widely spreading, ridged stems. Leaves are alternate, broadly ovate, hairy. Flowers are solitary and in leaf axils. Flower is wheel-shaped to short-funnel shaped, 1.5 - 2.5 cm across, and with 5 parts. Yellowish in color.

Geographical Location and Habitat

- *P. heterophylla* - Eastern North America, westward to Texas.
- *P. subglabrata* - Eastern North America, southwestward to Arkansas and Colorado.
- Both plants grow in meadows, pastures and old fields.

Toxic Principle

The glycoalkaloid solanine + atropine-like alkaloids.

Toxicity

- Generally avoided unless forage is scarce.
- Large quantities of the tops and unripe berries may cause toxicosis in animals.
- Unripe fruit is most toxic.
- The berries of **some** species are edible when raw or cooked.

Signs

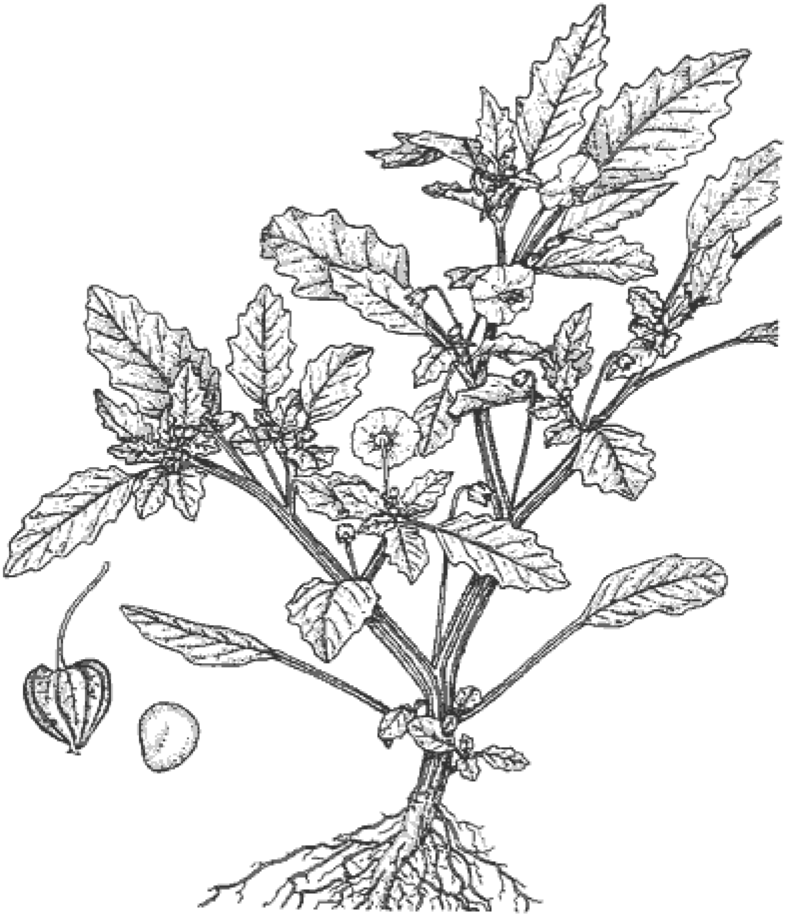
- Gastrointestinal upset, dyspnea, trembling, hyperthermia, weakness, and paralysis.
- Fatal poisonings have occurred in children.

Lesions

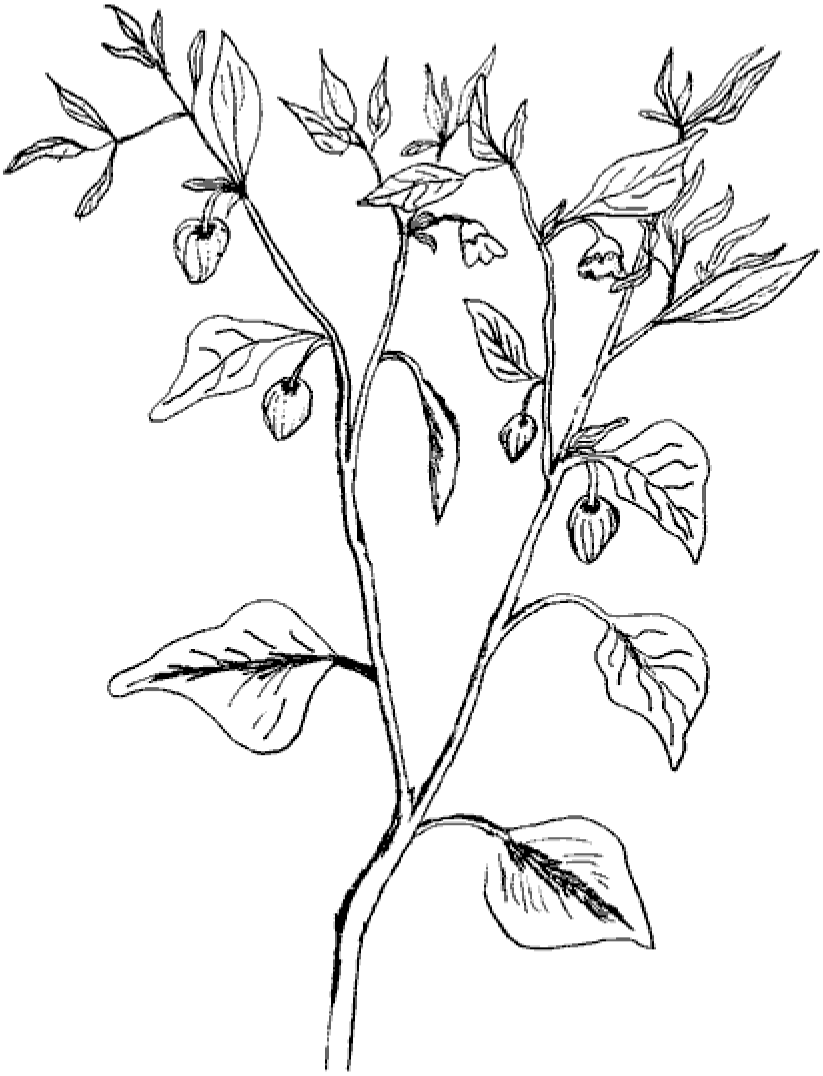
Gastrointestinal hyperemia, etc.

Treatment

- See *Solanum* and/or Introduction to Anticholinergic Agents section depending upon predominant signs.
- Fluid therapy and general supportive care as for gastroenteritis may be required.



Wright Groundcherry (*Physalis wrightii*) **-** The wavy-margined leaves, colorful flowers with flared openings, inflated seed pod (lower far left), and seed (enlarged, lower near left) characterize this southwestern forb.



Physalis subglabrata

Matrimony Vine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
All species	Minutes to hours	Hours to 3 days	

Family - Solanaceae

Species

- Box thorn, false jessamine.
- *Lycium halimifolium*
- *L. carolinianum*.

Description

A woody, upright shrub or vine with curving pendant branches, up to 10 feet tall. The numerous branches occasionally bear long woody thorns. Flowers are solitary or few. Has 5 pointed green, bell-shaped calyces and a 5-lobed violet flower with 5 stamens. Fruit is a small orange or red berry about 2 cm in length.

Habitat

- *L. halmifolium*: was used as an ornamental shrub, some may be present in older plantings; now escaped and naturalized locally in northern USA and southern Canada.
- *L. carolinianum*: native to southeastern United States from Texas to Florida, north to South Carolina.

Toxic Principle

- Solenaceous alkaloids; probably like the glycoalkaloid solanine.
- Leaves are poisonous.

Toxicosis

Rare.

Signs

- Excitement, convulsions, death.
- Severe gastroenteritis noted at necropsy.

Treatment

See *Solanum* section.

Matrimony vine
(Lycium halimifolium)

Cestrum spp. - Jessamines

Cestrum nocturnum - Night blooming jessamine
C. diurnum - Day blooming jessamine
Synonyms for both plants include Chinese inkberry.

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Pet animals	Minutes to hours	Hours to 3 days	

Family - *Solenaceae*

Description

- Large, handsome shrubs with alternate simple entire, most lanceolate or elyptical leaves and axillary clusters of fragrant showy, trumpet shaped, 1 inch long, 5 parted flowers.
- In *C. diurnum*:
    - The flowers are white and sweet scented by day.

    - Ovate leaves 5 - 10 cm long.
    - Mature fruit is a globose, black berry.
- In *C. nocturnum*:
    - They are greenish and sweet scented by night.
    - Mature fruit is white.
    - Have longer (10 - 20 cm long) leaves.

Habitat

Frequently used ornamentals in southern states. *C. diurnum* may also be found wild in the Florida Keys and south Texas.

Toxic Principle and Toxicity

- In the unripe berry, solanine (the gastrointestinal irritant/cholinesterase-inhibiting glycoalkaloid: see *Solanum*) predominates
- In the ripe berry and the foliage, tropane (atropine-like) alkaloids are most prevalent.
- Saponins or traces of nicotine possible.
- *C. diurnum* may contain toxic concentrations of 1,25-dihydroxyvitamin D-glucoside (see section entitled Vitamin D-containing Plants).

Susceptible Species

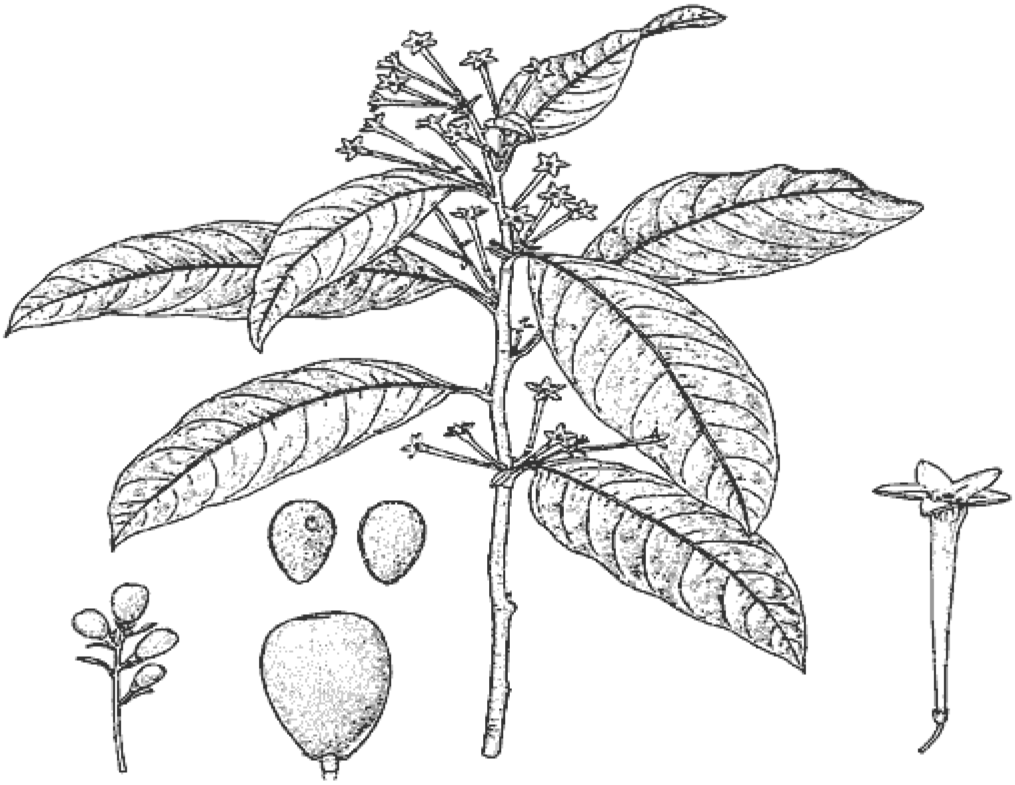
Humans, pets.

Signs

Signs can be referable to any of the three toxins involved and will vary with species of the plant involved and its age.

Treatment

See *Solanum* and/or Introduction to Anticholinergic Agents section depending upon predominant signs. Also, see section on Vitamin D-containing plants under the species (*C. diurnum*) and note the manifestations (e.g., due to hypercalcemia) that may occur.



Night-Blooming Cestrum - The attractive lance-shaped leaves, the fragrant greenish-white to cream-colored tubular flowers, the clusters of white berries (lower left), and the enlarged berry and seed (left center) characterize this tropical plant.

Solanum spp. - Nightshade Group

S. nigrum*, *S. americanum*, *S. ptycanthum - black nightshade, deadly nightshade, nightshade
S. tuberosum - Irish or white potato.
S. carolinense - horse nettle, Carolina horse nettle, bull nettle, treadsalve, sandbriar, thread softly.
S. elaegnifolium - silverleaf nightshade.
S. rostratum - buffalo bur, Kansas or Texas thistle.
S. dulcamara - European bittersweet.
S. gracile - graceful nightshade.
S. pseudocapsicum - Jerusalem cherry, natal cherry.
S. torreyi
S. triflorum - cutleaf nightshade.
S. villosum - hairy nightshade.
S. melangena - egg plant.
S. intrusum
S. aculeatissium (S. capsicoides) - devil's apple, sode-apple, love apple.
Lycopersicon - tomato.
S. malacoxylon - (see Vitamin D containing plants).

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Potato (*Solanum tuberosum*)	Herbivores	Minutes to hours	Hours to 3 days	
Black nightshade (*Solanum nigrum*)	Herbivores	Minutes to hours	Hours to 3 days	
Jerusalem cherry (*Solanum pseudocapsicum*) (may also contain cardiotoxic solanocapsine)	Herbivores	Minutes to hours	Hours to 3 days	
Tomato leaves, green fruit (*Lycopersicon*) (may also contain toxic amounts of nitrate)	Herbivores	Minutes to hours	Hours to 3 days; may also contain nitrate	

Family - Solanaceae

Geographical Location and Habitat

- *S. nigrum*.
    - Maine to N. Dakota, south to Florida, Louisiana and Texas; Canada and Europe. Waste areas, cultivated fields, around homes, disturbed fields and pastures, moist, open areas in woodlands, loamy or gravelly soils, roadsides and streambanks.
- *S. americanum*.
    - Florida and Georgia, west to California and south through South America as well as north and west to southern British Columbia.
- *S. ptycanthum*.
- *S. carolinense*.
    - Massachusetts to Nebraska, south to Texas and Florida, some western states (southern California). Overgrazed pastures, cultivated areas.
- *S. eleagnifolium*.
    - Missouri to Texas and California and south into Mexico.
- *S. rostratum*.
    - North Dakota to Texas, westward and south into Mexico. Old fields, overgrazed pastures, roadsides.
- *S. malacoxylon*.

    - Ubiquitous in much of Brazil and Argentina; also in Hawaii; occurs especially in areas prone to flooding, and in pastureland.
- *S. dimidiatum*.
    - Grows in Texas, west of the Colorado River. Note: This is not the major river of the same name that runs through several western states.

Description

- *S. nigrum*.
    - Climbing perennial herb reaching up to 3 m tall, but usually 0.3 - 1 m tall, annual, erect. Leaves are alternate, simple or deeply lobed, wavy-toothed or oval- to lance-shaped, stalked and long, 3.8 - 10 cm. Flowers are white with large yellow anthers, which extend from the leaf axils in small drooping clusters with 2 - 20 blossoms. Flowers are small (0.6 - 1 cm across) with 5 white or pale violet petals. Fruits are round, 0.6 cm thick, purple-black when fully ripened, green when unripe, and contain many seeds.
- *S. carolinense*.
    - Perennial herb, 0.3 - 0.6 m tall, with yellow spines on the stems and simple, oblong, irregular or lobed leaves. Flowers are pale violet or white. Fruits are yellow berries about 1.2 cm in diameter.
- *S. eleagnifolium*.
    - Perennial, 0.3 - 1 m tall, with a white hairy stem, and simple, thick, lanceolate to linear leaves with short, stiff spines. The leaves are silvery white in color. Flowers are violet or blue, and fruits are yellow or orange berries. Plant has long creeping rootstalks.
- *S. pseudocapsicum*.
    - A shrub or potted plant growing up to 1.3 m tall, with dark green, shiny, waxy leaves, oblong in shape and 10 cm long. Flowers are white, in clusters, or alone, and 1.2 cm wide. Fruits are globular, 1.2 cm in diameter, scarlet or yellow, and resemble miniature tomatoes.
- *S. malacoxylon*.
    - A shrub, up to 1 - 1.5 m tall, smooth with sharp pointed, lanceolate somewhat fleshy leaves on comparatively long stems.
- *S. dimidiatum*.
    - Perennial, 1 m tall, with short, rounded, leaves of 15 cm in length. Fruit are pale yellow berries of ~3 cm in diameter.

Toxic Principles

- Many contain the steroidal glycoalkaloid solanine. Upon hydrolysis, a sugar and the alkaloid solanidine are recovered. The free (unconjugated) steroidal alkaloid (the aglycone) is the primary form acting on the nervous system.
- Other aglycones present may include dihydrosolanidine, tomatidine and strophanthidin. Toxic properties of these compounds are characteristic of saponins. Some plants may also contain saponins.
- Some of these plants also have cardiac effects, e.g., Jerusalem cherry (*S. pseudocapsicum*) contains an additional alkaloid, solanocapsine, which produces bradycardia. The plant may also irritate the skin.
- In some plants, atropine-like constituents predominate, e.g., potato (*S. tuberosum*), and some strains and stages of black nightshade (*S. nigrum*).
- *Solanum malacoxylon* contains toxic amounts of 1,25-dihydroxycholecalcified glucoside section on Vitamin D containing plants for information on the toxic effects of this plant.
- *S. dimidiatum*
    - Toxic principle is unknown.

Toxicity

- Often poisoning occurs under conditions of overgrazing.
- Generally, the leaves and green fruits are toxic. The juice in the wilted leaves is especially toxic, and may be deadly if ingested. Many cases of poisoning have been reported as a result of eating green berries. Berries (green) have produced severe intestinal, oral and esophageal lesions in sheep. Cattle reportedly seek out the berries of *Solanum* and will eat the green plant, especially when other green forage is unavailable.
- Silverleaf nightshade (*S. eleagnifolium*) is exceptional in that the ripe fruit is more toxic than the green. *S. eleagnifolium* is toxic at only 0.1% of the body weight.
- Toxicity is not lost upon drying. Solanine content increases up to maturity.

- Solanine is reportedly destroyed by cooking except potatoes (see below).
- Potato (*S. tuberosum*) peelings contain the major portion of the toxic principle in the tuber, and leaves, sprouts, vines and especially sun-greened potatoes are toxic. Spoiled potatoes and peelings have also caused severe poisoning. Cooking does not appear to destroy all the alkaloids in greened potatoes. Toxicity may vary with the soil, climate and other variables. Animals may browse potato plants or eat sprouted potatoes, leading to problems. Potatoes containing over 0.02% of solanine are considered toxic to man. Several lethal toxicoses in human beings reported.
- Jerusalem cherry *(S. pseudocapsicum*) leaves and fruits have poisoned children, and may also cause dermatitis.

Mechanism of Action

- Solanine is a direct irritant of the esophageal and gastric mucosae.
- The steroidal alkaloids act as inhibitors of acetylcholinesterase although their potency in this regard, and thus the centrality of this mechanism is debated. Regardless; the alkaloids are clearly neurotoxic and often they cause ataxia and depression.
- Atropine-like alkaloids from some *Solanum* species competitively inhibit acetylcholine at muscarinic receptors.

Susceptible Species

Sheep, goats, calves, adult cattle, chickens, ducks, horses, rabbits, dogs, humans, swine (especially), and presumably other species.

Signs

- Clinical signs vary with the irritant effect caused by the intact glycoalkaloid or saponin, and the nervous effects of the alkaloid.
- Irritant effects include salivation, anorexia, severe gastrointestinal disturbances, with diarrhea that is often early and hemorrhagic.
- The nervous effects include apathy, drowsiness, depression, confusion, progressive muscular weakness, numbness, dilated pupils, trembling, labored breathing, nasal discharge, rapid heartbeat, weak pulse, bradycardia, CNS depression, and incoordination, often accompanied by paralysis of the rear legs. Coma may occur without other nervous signs.
- High doses may cause intestinal stasis and constipation.
- Hemolysis and anemia, possibly a result of saponins have been reported.
- Renal failure has been reported in severe cases.
- Terminal signs include unconsciousness, shock, paralysis, coma, circulatory and respiratory depression, and death.
- The course varies from sudden death to a course of 3 - 4 days which may terminate in death or recovery. In less acutely poisoned animals, there may be yellow discoloration of the skin in unpigmented areas, weakness, incoordination, tremors of the rear legs, anemia, rapid heart rate and bloat.

Lesions

- No lesions occur in some cases involving sudden death from large doses. In other animals, there may be edema around the kidneys, clots around the kidneys, and possibly pale kidneys which exhibit tubular necrosis when examined histologically. Gastroenteritis may be minimal or may include hyperemia, hemorrhage and ulceration of the alimentary tract. The liver may be congested and the gallbladder distended. There is sometimes edema of the ventral body wall and congestion and emphysema in the lungs. Hemorrhage and congestion may also occur in the heart and spleen.
- *S. dimidiatum* is unique among Solanacea in causing necrosis of Purkinje cells of the cerebellum.

Treatment

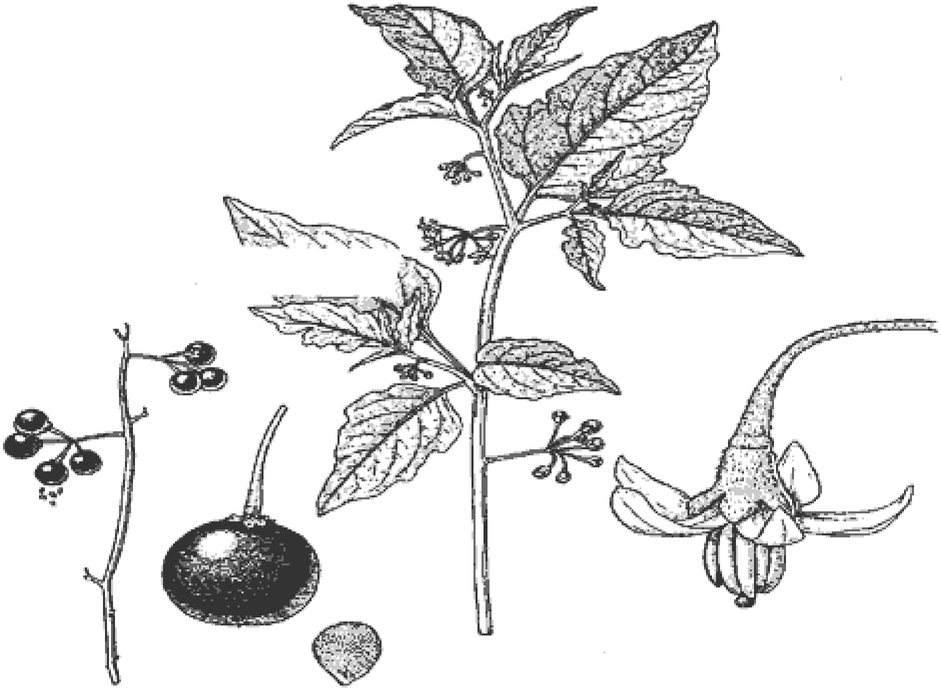
- Establish respiration, induce vomiting unless contraindicated, activated charcoal, saline cathartic.
- Symptomatic and supportive treatment. Maintain body fluid and electrolyte balance.
- Dermatitis may be relieved by washing with soap and water and application of corticosteroids.
- When life-threatening, atropine-like poisoning is suggested based on clinical signs, consider physostigmine therapy (as for atropine ingestion; see Introduction to Anticholinergic Agents section). If signs suggesting cholinesterase inhibition predominate, consider cautious (!) treatment with atropine.
- Cattle surviving 24 hours will generally recover.

Prevention

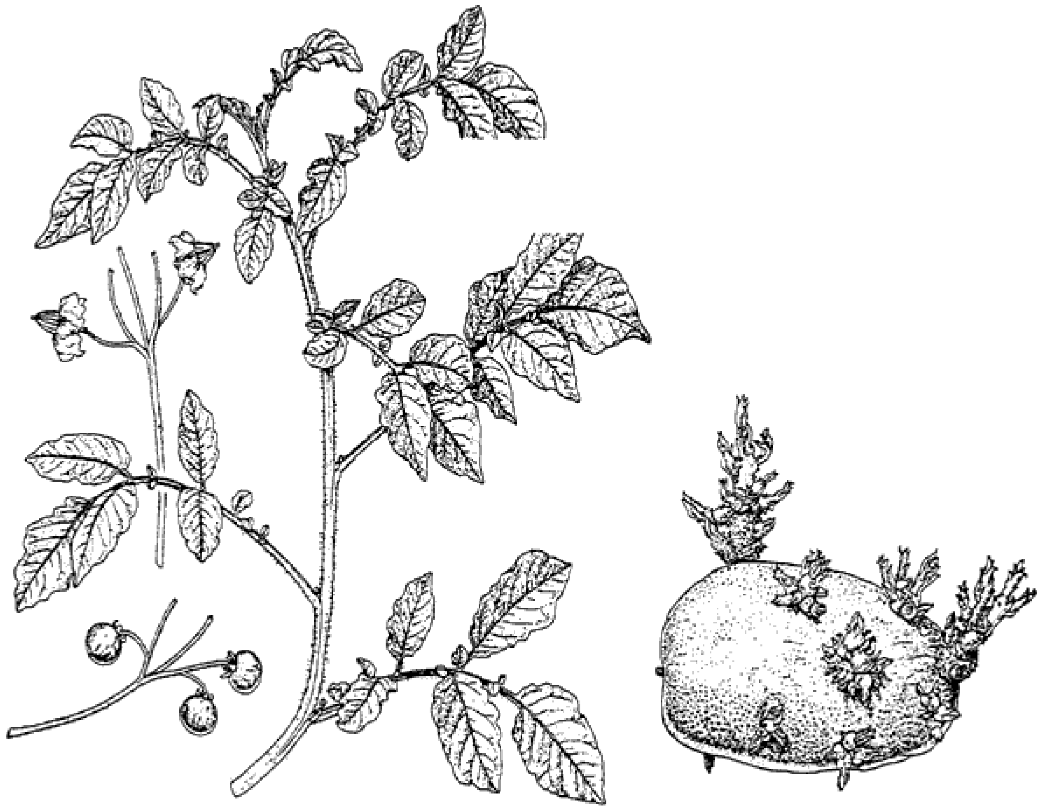
- The pasture should be mowed before the seeds ripen to control propagation of the weeds. Keep animals out of areas with heavily concentrated weeds, especially if forage is not abundant. Hungry animals should not be allowed to graze areas where an abundance of silverleaf nightshade is growing. Remove green parts of potatoes before cooking, eat only ripe tubers.
- Herbicides are sometimes used to help control nightshades.
- When in hay and animals are preferentially eating the other plants, consistent overfeeding of the hay and daily removal of the "wasted" (uneaten) poisonous plants may sometimes be an economic (but not risk-free) necessity.

Note

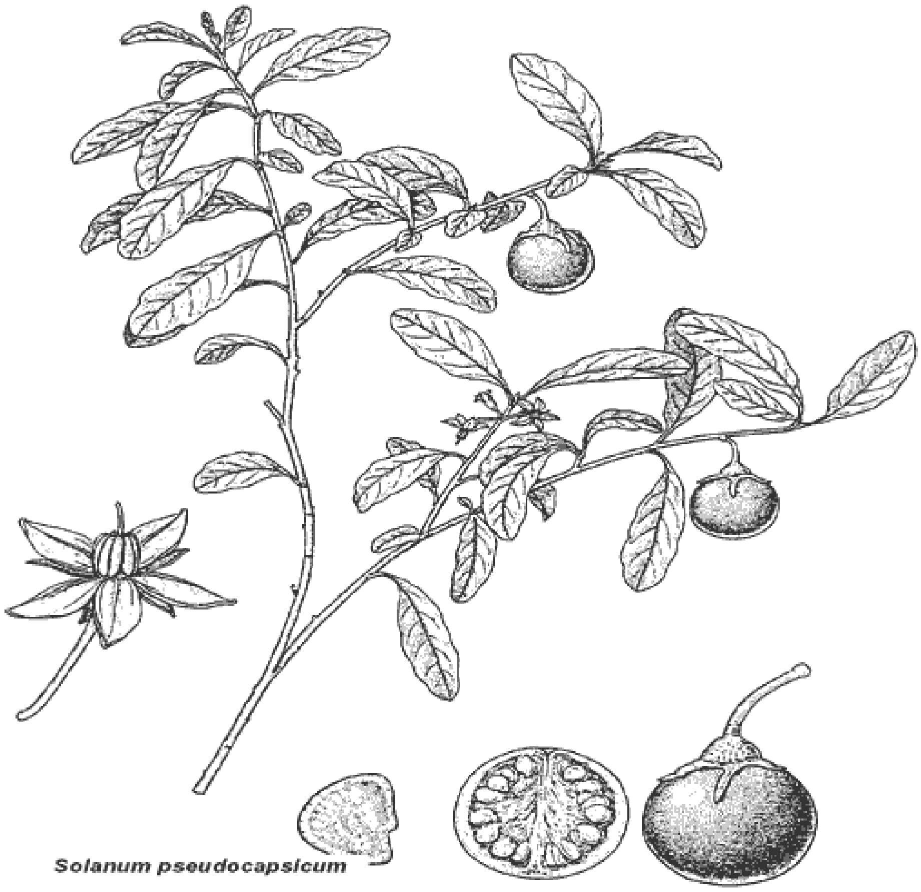
- Some of the lesions of *Solanum* toxicosis are occasionally similar to those of *Amaranthus retroflexus* (pigweed) poisoning.
- Do not confuse deadly or bittersweet nightshade (*S. dulcamara*) with climbing bittersweet (*Celastrus scandens*).



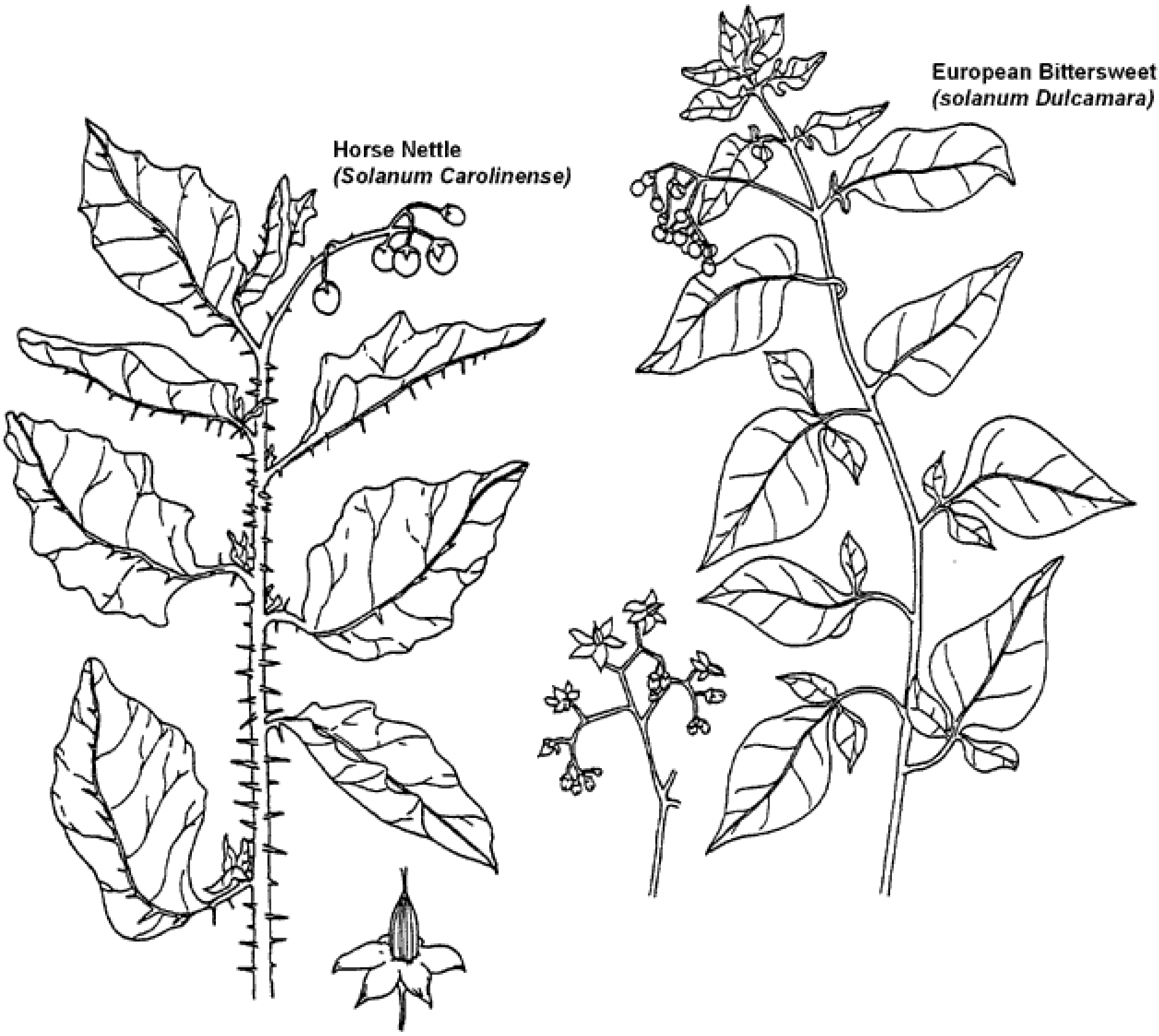
Black Nightshade - Note the entire to lobed leaves, the axillary flower clusters, the flower (enlarged, right), the clusters of berries, the berry (enlarged, left), and the seed (enlarged, lower center) of this dangerous herb.



Potato - The pinnelely divided leaves, the white or bluish flower (upper left), the yellowish or green berries (lower right), and sprouted tuber (lower left) are characteristic of this important, sometimes poisonous, food plant.



Jerusalem-Cherry - Note the oblong, wavy-margined leaves, the white flowers (enlarged, lower left), and the attractive berries (enlarged, lower right) and seeds (enlarged, lower center) of this ornamental plant.



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2. Toxicants with Muscarinic Effects but No Nicotine Effects

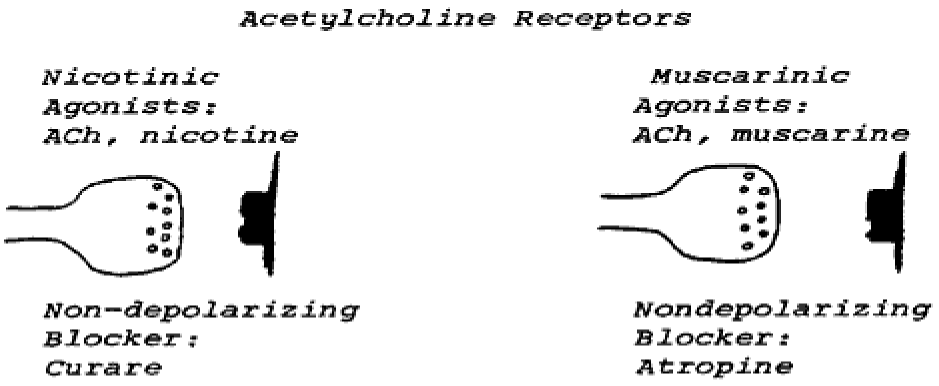
Introduction to Muscarinic Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
Pilocarpine	All species	Minutes	Hours; rarely lethal	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Arecoline (obsolete drug formerly used to treat small animals for tapeworms)	Dogs, cats	Minutes	Hours; rarely lethal	
Methacholine	All species	Minutes	Hours; rarely lethal	
Carbachol	All species	Minutes	Hours; rarely lethal	
Bethanechol	All species	Minutes	Hours; rarely lethal	

Muscarinic Receptors

- Postganglionic parasympathetic neuroeffector junctions.
    - Parasympathetic cardiac, parasympathetic smooth muscle, and exocrine gland innervation.
- Also present at some smooth muscle (e.g., arterioles) sites without cholinergic innervation.
- Cholinergic neuroeffector junction of the sympathetic nervous system (e.g., at ganglion).

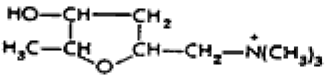
- Parasympathomimetic.



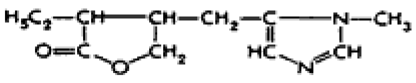
This section refers only to muscarinic agents. Recall, however, that there are 2 kinds of acetylcholine receptors: sites of action of muscarinic vs. those of nicotinic alkaloids. The synaptic endings shown both release acetylcholine (ACh). The postsynaptic membrane on the left responds both to ACh and to nicotine but not to muscarine. The response of the receptors can be blocked by curare. The receptors are described as nicotinic. The postsynaptic membrane on the right responds to ACh and to muscarine but not to nicotine. The response can be blocked by atropine. The receptors are called muscarinic.

Sources of Muscarinic Toxicants

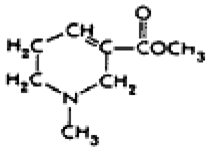
- Muscarinic Alkaloids.
  - **Muscarine** has been used to identify muscarinic receptors-not used as a drug. Originally isolated from *Amanita muscaria*; although usually not the primary toxic principle.
  - **Pilocarpine** is isolated from the Brazilian shrubs, *Pilocarpus jaborandi* and *P. microphyllus*. It is used as a **miotic**. Can have systemic effects, e.g., anomalous cardiovascular responses. Used therapeutically for glaucoma and other ophthalmic conditions requiring miosis. Especially effective at stimulating exocrine gland secretions.
  - **Arecoline** is the primary alkaloid from *Areca catechu*, or betel nut (East Indies).
    - Potent stimulant of gastrointestinal motility (e.g., has been used for **tapeworm removal**).
    - Acts to a lesser extent at nicotinic **receptors**.



Muscarine



Pilocarpine



Arecoline

- **Muscarinic Choline Esters**.
  - **Acetylcholine itself**.
  - **Methacholine**.
  - **Carbachol**
    - Especially GI and urinary tracts.
  - **Bethanechol**

Signs

- **Muscarinic Signs**.
  - Colic, can be severe, diarrhea, vomiting.
  - Visual disturbances, miosis.
  - Hypotension and bradycardia (mediated via vagus). Severe bronchospasm and bronchial secretions can cause death.
  - Shock.

    - Exocrine secretions including salivation and lacrimation.
    - Exposure to arecoline or systemic exposure to pilocarpine is contraindicated in animals with heart failure, depression, or spasmodic colic, as well as during gestation.

Treatment

- **Atropine**-Repeat as needed. Dose to effect as for organophosphorus insecticide toxicosis.
- Evacuate gastrointestinal tract if oral exposure has occurred.
- Activated charcoal.

Muscarinic - Histaminic Mushrooms

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Mostly pet animals	30 minutes to hours	Hours to 2 days; rarely lethal	

Mushrooms

Boletus eastwoodae, Boletus luridus, Boletus satanas, and possibly other species of *Boletus* with red pore mouths. *Clitocybe cerussata*, var. difformis, *Clitocybe dealbata*, *Clitocybe illudens, Clitocybe rivulosa, Inocybe fastigiata, Inocybe geophyilla, Inocybe lilacina, Inocybe patuoillardi*, *Inocybe pudica*, and possibly others.

Pharmacology

L(+)muscarine and other less potent cholinergic compounds. Because of its quaternary configuration, muscarine does not cross the blood brain barrier to the central nervous system. Therefore, the cholinergic effect is entirely peripheral. Some of the muscarinic compounds have more of a histaminic effect with flushing, hypotension and asthmatic wheezing.

Signs

Onset within 30 - 120 minutes. Excessive perspiration (humans), salivation, and lacrimation, miosis, blurred vision, bradycardia, and increased peristalsis with crampy abdominal pain; and watery stools. These are followed by reduced blood pressure, pulmonary congestion and asthmatic wheezing. **Note** - The perspiration-salivation-lacrimation combination reportedly does not occur in other types of mushroom poisoning.

Toxicity

Fatality rates for poisoned humans range from 6 - 12%. Most deaths occur in children with cardiac or pulmonary disease.

Diagnosis

Muscarine has been detected in urine and can be used for confirmation of this type of poisoning. Effective treatment should be instituted on the basis of clinical signs and history before any laboratory work is available. Response to therapy helps to confirm the diagnosis.

Treatment

- Prevention of absorption:
    - Emesis should be initiated unless the patient is comatose, convulsing, or has lost the gag reflex.

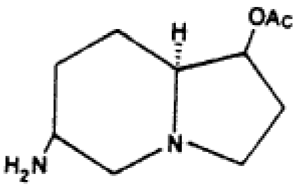
  - If contraindications to emesis exist, intubation should precede gastric lavage.
  - Emesis may not be of further value if the animal has already vomitted repeatedly.
  - Activated charcoal is recommended at 5 - 10 times the estimated ingested dose or 2 g/kg in a water slurry.
  - Sodium sulfate 250 - 500 mg/kg/orally as a cathartic in a 20% or more dilute aqueous solution.
- Atropine.
  - Should be administered if life-threatening cholinergic symptoms exist. An atropine test dose of 0.05 mg/kg should be administered. If the patient is poisoned, no signs of atropinism (e.g., tachycardia, dry mouth) will develop; and the atropine dose may be increased and repeated as needed. The endpoint is cessation of excessive bronchial secretions, and especially ease of breathing, **not** dilatation of pupils and not cessation of salivation.
  - Supportive care with intravenous fluids may be necessary.

Slaframine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Cattle, horses, sheep	Hours	Up to 3 days; unlikely to be lethal	

Source

- Slaframine or "slobber factor" is an indolizidine alkaloid mycotoxin produced most often in red clover *Trifolium pratense* infected by the fungus *Rhizoctonia leguminicola*, which is the cause of "black patch" of this and other legumes. The toxin is sometimes also present in other legume forages contaminated by this mold.
  - The parent compound, slaframine, has no activity but is transformed in the body to a quaternary amine (ketoimine) which is chemically (and to some degree physiologically) somewhat similar to acetylcholine.
  - *R. leguminicola* can survive over 1 - 2 seasons in red clover seed.
  - Moist weather precedes the occurrence of "slobber factor" in toxic concentrations.
  - The production of slaframine is decreased at temperatures over 25 ºC.
  - No resistant strains of red clover have yet been found.
  - Occasionally slaframine may be produced in other types of legume forages.
  - The toxin is a constituent of the fungus rather than an "exotoxin".



Slaframine

Mechanism of Action

- Cholinergic stimulation of exocrine glands (actually mimics ACH at the receptor, rather than causing ACH release).
- No effect on ganglionic transmission, peripheral blood flow or neuromuscular transmission.
- At reasonable doses, there is no change in heart rate, respiration, or blood pressure.

Susceptible Species

Toxicosis is most commonly reported in cattle, horses, and sheep. Goats may also be affected, but other species have been demonstrated to be susceptible including: swine, chickens, guinea pigs, rats, and mice.

Toxicity

In LA, signs begin after 5 - 15 # of affected red clover has been eaten.

Signs

- May occur 30 - 60 minutes after first consumption of affected hay. Some sources suggest that they generally occur after a latent period of 4 - 6 hours postingestion. Clinical signs intensify up to 24 hours postexposure, and condition usually resolves within 96 hours after the last feeding of the contaminated hay.
- Clinical signs may last from 6 - 8 hours in small laboratory animals.
- Excessive salivation is usually the first sign.
- Lacrimation, rarely severe.
- Anorexia (sometimes animals refuse to eat more of the contaminated forage).
- Diarrhea, sometimes watery.
- Frequent urination.
- Bloat.
- Decreased milk production.
- Abortion.
- Stiffness.
- Death has been reported in cattle.
- The principle economic losses are associated with reduced production and feed replacement costs.
- Horses with significant toxicoses have been observed to salivate, so severely, that after being tied to a post for a few minutes a puddle of saliva accumulates in the soil beneath their heads. These horses were consuming a stemmy, black hay, barely identifiable as to the plants contained but identified as red clover hay. In spite of the severe salivation, the horses were being ridden repeatedly on a horse-for-hire basis and did not appear to experience other adverse effects upon casual observation.

Lesions

- Guinea pigs:
    - Experimentally dosed animals had pulmonary hyperemia, edema, and emphysema. Liver and kidney congestion.
    - Tracheal submucosal eosinophilia was noted but its significance and consistency are not known.
- Pregnant rats:
    - Uterine hemorrhage and abortion.
- Pregnant cattle and horses:
    - Occasional abortions reported.

Diagnosis

- SLUD: salivation, lacrimation, urination, defecation (all muscarinic signs), but may see only salivation.
- Usually red clover in the diet is second cutting hay.
- Presence of dark brown mycelium in the hay or on the pasture plants.
- The mycelium is very much larger than most other fungi.
- Confirm by identifying the *R. leguminicola* in the forage or by bioassay.
- May get false negatives from attempts to culture the fungus.
- Bioassays:
    - Guinea pig bioassay (feed test).
    - Finely grind red clover, especially stems, and mix with equal parts of ground guinea pig pellets. Feed at least 1 week and check daily for salivation.
    - Guinea pig bioassay (fungus test for toxigenic potential).

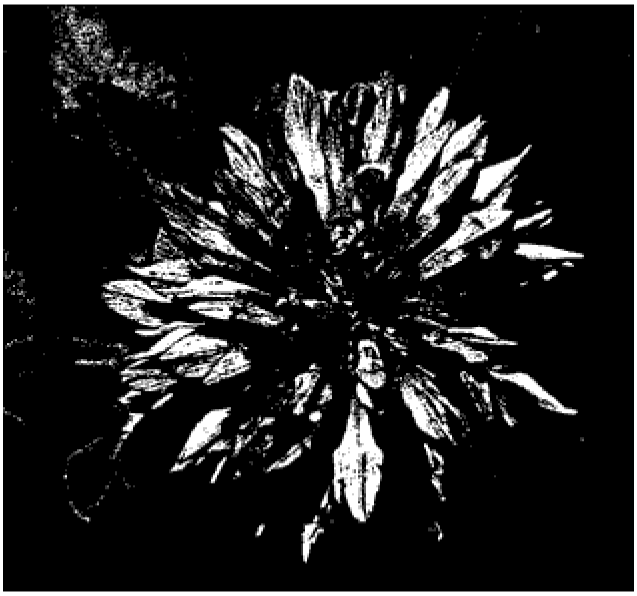
        - Isolate *R. leguminicola*, and cultivate on extracts of red clover **not** other substrates. Force feed mycelium to guinea pigs.
        - Salivate in 60 minutes.
        - **Note** - culture filtrates are not toxic.
        - Alternatively, can extract mycelium from fungus with chloroform at a pH between 7 and 10 (higher will hydrolyze slaframine), dry, dissolve in saline, adjust pH to neutrality and inject guinea pig IP. A positive test result is comprised of salivation in 10 - 30 minutes.
    - Bovine (feed test).
        - Grind up and administer into a fistulated cow.
        - Salivation, epiphora, diarrhea and/or other cholinomimetic signs comprise a positive response.
- Direct identification of slaframine in toxic hay is possible:
  Confirmation of slaframine can be obtained by submitting suspected hay or legumes in pastures to the Diagnostic Laboratory at the College of Veterinary Medicine of Iowa State University at Ames, IA, USA.

Treatment

- Remove from source. Most animals will recover.
- Will take 2 - 3 days for affected animals to respond.
- Symptomatic treatment in severely affected animals.
    - Atropine not very effective unless given before slaframine.
    - Therefore slaframine must have greater affinity for receptor than atropine.
    - Antihistamines reported to be effective.

Note

R. leguminicola may also produce swainsonine, which is structurally - somewhat similar to slaframine. Swainsonine is the toxic constituent of "true locoism" in *Astragalus* and *Oxytropis* spp. Whether the amounts present in red clover are sufficient to cause clinical or histologic changes similar to those in true locoism seems unlikely.



Red Clover (*Trifolium pratense* L.)

3. Inhibitors of Cholinesterase

Organophosphorus and Carbamate Insecticides

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Organophosphorus insecticides and avicides	All species	Minutes to hours	Days to 4 weeks; often lethal	
Carbamate insecticides	All species	Minutes to hours	Hours to 1 day; often lethal	

Organophosphorus (OP) insecticides are often referred to as organophosphates, which is actually a misnomer (they are not salts).

- Most are applied to surfaces of plants, animals, soils, or household floors, etc.
- Others are systemics:
    - Absorbed via any route by plants or animals and distributed through the organism on which the insect pest feeds.
- The most prevalent and toxic chemical warfare agents are potent OP compounds (soman, sarin, tabun). These compounds are not used as insecticides.

Carbamate insecticides, which are derivatives of carbamic acid are used for similar surface applications.

- The original carbamate, physostigmine, is a plant alkaloid, derived from the "ordeal bean" (see Introduction to Anticholinergic Agents section for therapeutic uses of physostigmine).

Both OP and carbamate groups contain members comparatively low in toxicity and others which are extremely poisonous.

Sources

Feed-Related Problems: (80% of all exposures in food animals).

- Misidentification of granular pesticides as vitamin or mineral supplements.
    - Aldicarb granules are black to grey outside; beige inside.
- Adjacent storage of feed ingredients and pesticides.
- Use of vehicles to transport pesticides prior to transporting feed.
- Accidental or excessive application to forage crops.

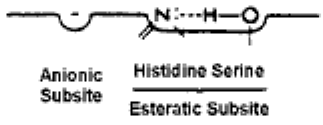
Other Sources

- Miscalculation of dosage during spraying, dipping, oral dosage.
- Exposure of animals to products intended for other species (e.g., cats treated with dips for dogs).
- Exposure of pets to insecticidal products applied to the home.
- Use of insecticides on stressed animals.

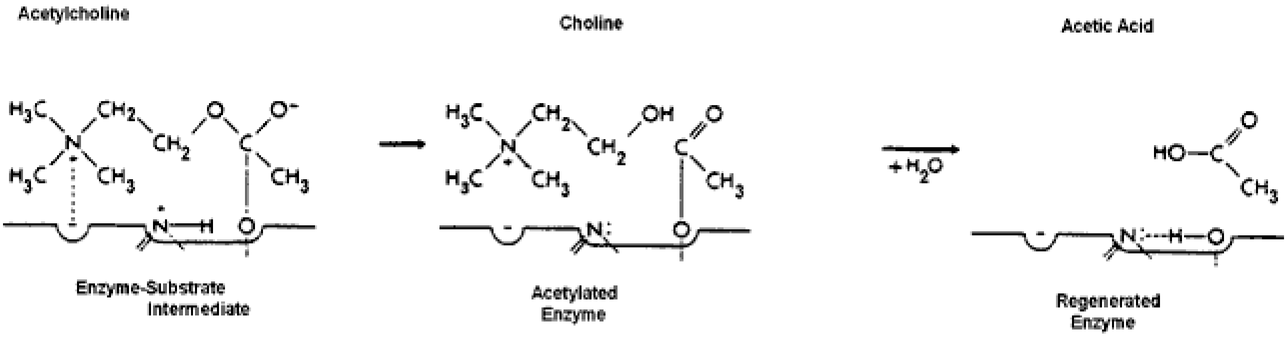
Mechanism(s) of Action

- Acetylcholine (ACH) is the mediator at junctions including those between:
    - Preganglionic and postganglionic neurons in both parasympathetic and sympathetic nervous system.
    - Postganglionic parasympathetic fibers and smooth muscles or glands.
    - Motor nerves and skeletal muscles.
    - Some neuron to neuron junctions in the CNS.
- Acetylcholinesterase (ACHE) also known as true cholinesterase is the enzyme that rapidly hydrolyzes ACH at these locations.
    - Red blood cells contain primarily ACHE and plasma contains pseudocholinesterase. The actual physiological purposes of the enzymes located in blood are unknown.

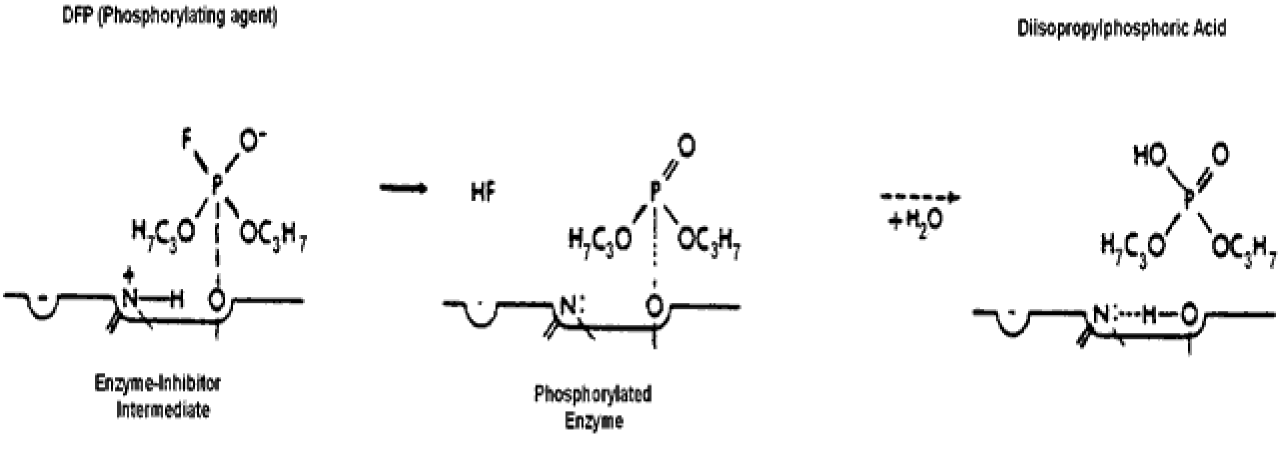
- During its action, acetylcholinesterase is very temporarily bound to the acetyl and choline ends of the molecule until hydrolysis and release of choline and acetate occurs. Prior to the release of the acetate (which is released last), the enzyme is, for an instant, "acetylated".



Acetylcholinesterase Active Center



- Binding of acetylcholinesterase by a carbamate insecticide is generally followed by hydrolysis of the insecticide, but the enzyme remains temporarily carbamylated and thus inhibited. The binding, and associated inhibition, is generally reversible, but often lasts long enough to allow clinical signs and sometimes death to occur.
- Organophosphate and carbamate insecticides competitively inhibit both acetylcholinesterases and pseudocholinesterases.
- The binding of acetylcholinesterase by different organophosphous inhibitors varies somewhat in affinity and reversibility. After binding, the enzyme is "phosphorylated", and thus inhibited. Generally speaking, much of the binding of ACHE by an OP is regarded as "irreversible".
- With some of the OP compounds, after binding to acetylcholinesterase, a chemical change in the OP takes place which significantly strengthens the attachment of the phosphorus to acetylcholinesterase. This is referred to as "*aging*" of the insecticide, and it occurs to different degrees and at different rates with various OPs. After aging, treatment by oximes is not effective in reversing the binding of the OP.
- Some OPs (especially those with a -P=S moiety) require metabolic oxidation to form a -P=O before they effectively inhibit acetylcholinesterase.


DFP (Phosphorylating agent)
Diisopropylphosphoric Acid
HF
+H₂O
Enzyme-Inhibitor Intermediate
Phosphorylated Enzyme

  - As a result of phosphorylation or carbamylation, the acetylcholinesterase enzyme ceases its normal function and acetylcholine concentrations at neuroeffector sites build up, resulting in continuous stimulation of nervous, glandular, or muscular receptors.
  - Different cholinesterase inhibitors have additive effects.
  - Phenothiazine and derivatives as well as other agents including some quaternary ammonium bases may also inhibit cholinesterases, potentiating the toxicity of the insecticide.
  - Cholinesterase inhibitors potentiate succinylcholine by inhibiting pseudocholinesterase, by which it is normally hydrolyzed. This can produce a profound increase in the intensity and duration of succinylcholine-induced respiratory paralysis.
  - Death due to OP or carbamate toxicoses is usually due to one or more of the following effects:
    - Increased respiratory tract secretions and bronchiolar constriction with hypoxia aggravated by bradycardia.
    - Respiratory depression from nicotinic stimulation to the point of paralysis.
    - Respiratory paralysis from CNS depression due to central effects of the insecticide (may be the primary cause of respiratory failure in some species).

Signs

- 3 categories of effects occur in poisoned animals: muscarinic, nicotinic, and central nervous system effects.
- Muscarinic:
  - Salivation.
  - Gastrointestinal hypermotility, pain, vomiting, and diarrhea.
  - Lacrimation.
  - Miosis (or mydriasis perhaps attributable to epinephrine release).
  - Dyspnea (bronchial secretion, constriction) and resultant cyanosis.
  - Micturition.
  - Bradycardia (or tachycardia perhaps attributable to epinephrine release).
- Death may result from hypoxia, which results from bronchial secretions, bronchoconstriction, and an erratic, slowed heartbeat.
  - Horses-colic, abdominal pain, salivation, severe diarrhea (often watery), dehydration.
- Nicotinic:
  - Stimulation of skeletal muscles:
    - Twitching of facial muscles, eyelids, tongue, and eventually the general musculature.
    - Generalized tetany.
    - Subsequent weakness and paralysis, possibly respiratory paralysis and death.
- Central nervous system:
  - Vary with species: severe CNS depression common in any species.
    - Food animals-often exhibit hyperactivity.
      - Rarely if ever, seizure.
    - Dogs and cats-occasionally seizure.
      - Hyperactive.
      - Hyperreflexive.
  - Centrally mediated respiratory paralysis (may be lethal).
- Specific OP characteristics.
  - Coumaphos, a systemic, may cause a syndrome with a slower onset, muscarinic and nicotinic signs including tetany and seizure prior to death.
  - Crufomate (Ruelene)-another systemic causes early rigidity and ataxia and later depression and muscarinic effects.
  - Chlorpyrifos (Dursban 44)-pour on in bulls and exotic beef breeds.
    - Maximal (topical) dose (16 ml) is for 800# (animals larger than 800# all get same dose as an 800# animal). Bulls of 2200# may die from the 800# dose (7 mg/kg).
    - Signs of chlorpyrifos toxicosis in cattle include anorexia, diarrhea, rumen stasis with fluid accumulation, dehydration, and death. Effects in topically exposed cattle may persist for days to a few weeks.
    - Cats: minimum lethal dose (oral) in cats (a highly sensitive species) of approximately 40 mg/kg.
      - Lethal toxicosis often results from the inappropriate use of dog flea dips containing chlorpyrifos on cats.
      - Signs in cats include: depression (occasional aggression), anorexia, salivation, vomiting, diarrhea, ataxia, tremors, and dyspnea. The depression and anorexia

        in topically exposed cats may persist for days to a few weeks. Orally exposed cats may recover in a few days.
        - May produce delayed neuropathy, at least in heavily exposed cats.
    - Ronnel-weakness in rear limbs, dragging of hind feet when walking, may last for up to several weeks.
    - Diazinon causes problems, especially in small animals and birds. Commonly used on lawns. It has been recently banned in golf course use.

Lesions

- Nonspecific.
- Salivation.
- Bronchial secretion or pulmonary edema.
- Occasional hemorrhages in gastrointestinal tract serosa and mucosa.

Residues

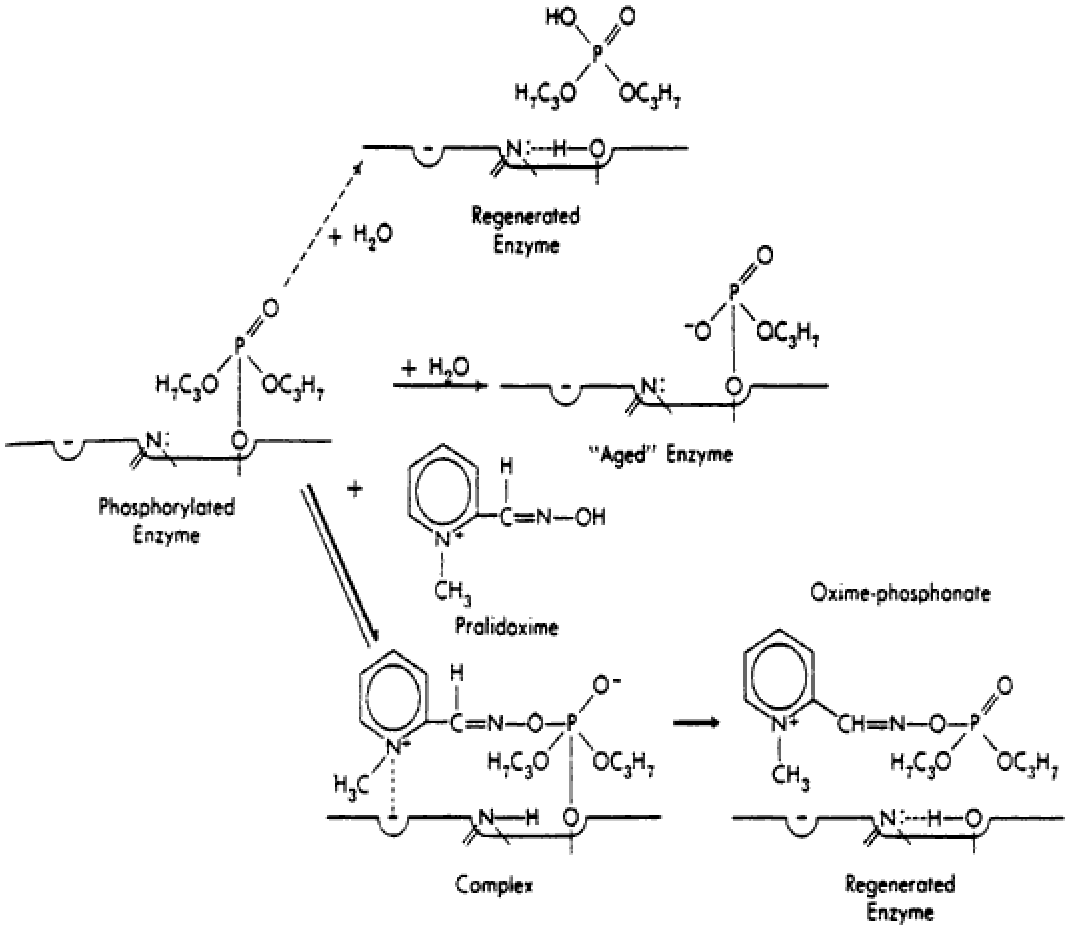
- Vary with the specific compound, degree, and route of exposure.
- Generally the carbamates cause comparatively little concern in the overall environment (on a broad scale) or in animal tissues, although aldicarb can be a problem in water, including ground water, and on vegetables (aldicarb in watermelons, 1985 in California).
- The OPs tend to be much less persistent than the organochlorine insecticides.

Diagnosis

- Excessive exposure and appropriate clinical signs.
- Reduced whole blood cholinesterase activity may suggest exposure to an organophosphate or carbamate and, although, **not a conclusive test**, should be performed on animals presented alive. In most species whole blood cholinesterase is considerably less sensitive than pseudocholinesterase. Therfore, depression of the activity of whole blood cholinesterase is more indicative of serious exposure or toxicosis than plasma pseudocholinesterase. Conversely, plasma pseudocholinesterase is a more sensitive test for detecting exposure than whole blood cholinesterase. It is possible to have no plasma cholinesterase activity detected in animals exposed to therapeutic (parasiticidal) amounts of OPs.
- In most species, the red blood cells contribute the major fraction of the activity in total blood cholinesterase.
- In most instances, the whole blood cholinesterase values of lethally poisoned animals fall below 25% of control values.
- In the cat, plasma pseudocholinesterase accounts for the vast majority of whole blood cholinesterase. Thus, the cat is very sensitive to depression of the total blood activity, even after exposures to amounts well below those capable of causing clinically evident toxic effects.
- Brain cholinesterase is very important in assessing the probability of poisoning in dead animals (obtain as soon as possible-right away after death, freeze, ship so that specimen remains frozen).
- Because the incubation time allows for decarbamylation, the Michel method of cholinesterase analysis may give false negative (false normal) values for carbamate toxicoses.
- Testing blood or homogenized brain tissue for cholinesterase activity at several times before and during a period of laboratory incubation can be used to differentiate an OP toxicosis (minimal or no regeneration of activity) from a carbamate (substantial regeneration of activity and potentially even full toxicosis recovery to normal values).
- Internal organs (e.g., liver) of poisoned animals may contain detectable residues of organophosphorus insecticides. Also, most of the compounds (OPs and carbamates) may be found in significant concentrations in skin and subcutaneous tissue after topical exposure.
- Stomach or rumen contents are often important in confirming diagnoses after oral exposure because the insecticides are often detected in these samples (ship frozen).
- There is a field screening test to detect cholinesterase inhibitors in air, water, soil, crops, spills, surfaces, solvents and other samples (Neogen Corporation, Lansing, MI).
- Test dose of atropine: try a preanesthetic dose of atropine and, if normal atropinization occurs at this dose (normal extent and duration of rapid heart rate, dry mouth and mydriasis), it tends to rule out poisoning from a cholinesterase inhibitor.

Treatment
Urgent

- Very early, emetics (only for very recent exposures; never when contraindicated and never when constant monitoring will not be undertaken).
- Activated charcoal (for any recent oral exposure) administered with appropriate precautions to avoid aspiration.
- Thoroughly bathe with detergent all animals exposed topically-taking care to avoid exposure of human skin. Use thick rubber gloves, plastic aprons, etc.
- Atropine sulfate (generally avoid use of charged agents, such as atropine methylnitrate or glycopyrrolate, which do not effectively enter the central nervous system).
    - Atropine sulfate-dosages higher than preanesthetic doses are routinely required for acute toxicoses (OP or carbamate).
    - Small animal products may contain atropine sulfate at 0.5 or 0.54 mg/ml; large animal products may contain 2 or 15 mg/ml.
    - May want to avoid atropine sulfate altogether in horses due to gut stasis, (except with life-threatening pulmonary or cardiac effects). When used in horses, atropine is added to fluids and administered IV while ausculting the abdomen. Administration is stopped prior to a reduction (to less than normal) in gastrointestinal sounds.
    - Suggested dose cattle 0.2 - 0.5 mg/kg. One-third of dose administered IV, the remainder given SC or IM.
    - Atropine is repeated judiciously as needed; but avoid gut and rumen atony. May be required at 4 - 8-hour intervals.
    - Suggested dose SA and birds 0.2 mg/kg. Some rabbits have atropinase and may require higher dosing, begin at 1.0 mg/kg but may need to increase to 10 mg/kg.
    - In all cases, subsequent doses of atropine should depend on the reappearance and severity of clinical signs. Clinical signs to use for monitoring include degree of respiratory distress, cyanosis, and heart rate. Effects such as miosis and salivation, which are not of concern in survival, are not used as therapeutic end points for atropine administration.
- Oximes.
    - Protopam (2 PAM), Pralidoxime hydrochloride, or TMB-4 act on the OP-ACHE complex to free the enzyme to resume its normal function if aging has not occurred and to enhance excretion of the insecticide. Not clearly proven of any benefit in carbamate toxicoses. Based on early, but since disputed data, it is often stated that 2-PAM is contraindicated in carbamate poisoning. However, when in doubt as to whether an insecticide poisoning is due to an OP or a carbamate, but signs suggest a cholinesterase inhibitor, an oxime should be used. Oximes are usually repeated BID. Protopam is given IM or IV at 20 mg/kg BID and continued, for days to weeks if necessary, until nicotinic signs resolve. If no response is apparent after 4 doses, the value of additional 2-PAM is in doubt and use of the drug should probably be discontinued. Cattle and horses can be dosed at 10 - 20 mg/kg.
    - Topically administered organophosphorus insecticides may be absorbed into the skin and/or subcutaneous fat before systemic distribution. Thus, absorption from these sites (skin, fat) may occur over several days time, and "aging" of the insecticide on the cholinesterase enzyme may not have occurred so that oximes may still be of benefit in these cases-even days after the initial exposure.
    - 2-PAM is generally of low toxicity. Overdoses can be associated with tachycardia, cardiac arrhythmias.
    - The maximum shelf-life of reconstituted 2-PAM is two weeks.



- Artificial respiration may be needed to counteract respiratory paralysis. Severe bronchospasm may be responsive to theophylline therapy. Older literature, however, suggests theophylline may increase occurrence of seizures in OP toxicosis. It is essential to avoid hypoxia.
- Scopolamine maybe of value when severe CNS depression is not responsive to atropine therapy, but this is not widely accepted.
- Diphenhydramine has been recommended at 1 - 4 mg/kg per os every 6 - 8 hours to help control persistent nicotinic signs.
- Seizures may be controlled with diazepam or barbiturate anticonvulsants.
- Systemic acidosis may complicate OP or carbamate poisoning. Counteracting respiratory failure with atropine and/or assisted ventilation are recommended for respiratory acidosis. Sodium bicarbonate administered at an initial dose of 5 mg/kg IV can be used to correct metabolic acidosis. Subsequently, IV doses at 1 - 3 mEq/kg may be required. Monitor acid base status.
- Animals should be monitored for the development of chemical pneumonitis due either to aspiration of hydrocarbon solvents (when such formulations are ingested) or for aspiration of gastric contents.
- Stress of OP or carbamate toxicosis may predispose animals to secondary clinical problems: e.g., hemobartonellosis, reported in OP-poisoned cats.
- If prolonged administration of high doses of atropine is anticipated, it is best to avoid preparations containing benzyl alcohol preservatives in species/ages (e.g., cats and all neonates) susceptible to benzyl alcohol-related toxicosis (see section on Benzyl alcohol).

Delayed Neurotoxicity (Neuropathy)

Certain OPs may cause a polyneuritis with paresis or paralysis primarily of the hindlimbs with degeneration of axons and myelin in the medulla, spinal cord, and peripheral nerve. This effect is not caused by acetylcholinesterase inhibition. One should be aware that for at least a few OPs including EPN, animals surviving acute poisoning as a result of therapeutic intervention may exhibit delayed neuropathy beginning a few weeks after the acute syndrome. Certain OPs, almost nontoxic with regard to acute poisoning, readily produce delayed neuropathy at low, otherwise non-toxic dosages. Most new OPs are evaluated in hens (the preferred test animal) for their ability to cause delayed neuropathy prior to marketing. This is discussed further under the heading "Toxicants Causing Paralysis".

Anabaena flos-aquae - Blue-Green Algae

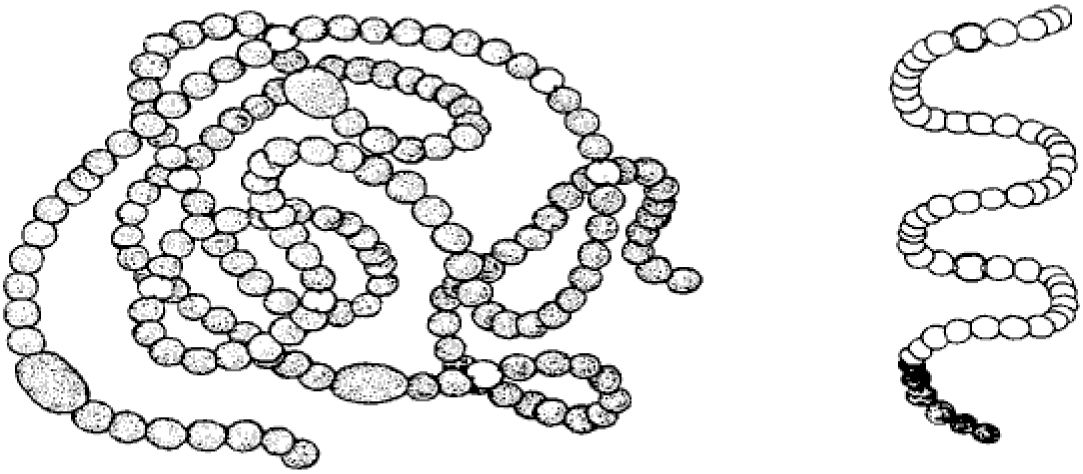
Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
All species	Minutes to hours	Days; often lethal	

Habitat

Warm, sunny weather generally preceeds a "bloom" of blue-green algae (also called cyanophytes or cyanobacteria). Usually, significant growth occurs in ponds or lakes which accumulate runoff from fields that are heavily fertilized or that receive the runoff from lots or pastures bearing significant numbers of animals. An abundance of phosphorous in the water usually accompanies blooms. Poisoning is most likely when animals have access to the water in an area of a wind-concentrated bloom.

Description

- Macroscopically blooms consist of a "scum" on top of water, blue, blue-green or green in color. Has no macroscopic filaments or other organization.
- Microscopically chains of cells including primarily vegetative cells sometimes with lesser numbers of spores and/or heterocysts. Cells are approximately the size of erythrocytes.



Anabaena flos-aquae and ***A. spiroides* var. *crassa* Lemm.**
Note - *A. flos-aquae* can also take this form.

Toxic Principles

- **Anatoxin-a**: a nicotinic depolarizing alkaloid neurotoxin is produced by some *A. flos-aquae* and some *Oscillatoria aghardii* blooms. Extremely potent and fast acting.
- Both *Oscillatoria* and less often *Anabaena* may produce algal peptide hepatotoxins (see Microcystins).
- **Anatoxin-a(s)**: the only known naturally occurring organophosphorus cholinesterase inhibitor: (s stands for salivation) is produced by some *A. flos-aquae* blooms.
- May also produce saxitoxin or neosaxitoxin. These act by blocking sodium channels. These toxins also cause paralytic shellfish poisoning.

Signs

- Anatoxin-a poisoning is similar to succinylcholine overdose. Animals may show rapid onset of rigidity and muscle tremors, then paralysis, cyanosis, and death due to respiratory paralysis. The onset of death may occur very rapidly. For example, when a bloom containing anatoxin-a was present in a South Dakota lake in early September 1985, a dog jumped in the water, swam out, but died before it could swim back to shore. The dog had apparently swallowed a small amount of the algae.
- Anatoxin-a(s) [Note the (s) is for salivation] toxicosis results in cholinesterase inhibition and thus a build up of acetylcholine which causes excessive salivation, gastrointestinal hypermotility, diarrhea, urination, and (at least in mice) an excessive amount of ocular mucus production. In lethal cases, however, the nicotinic effects of this cholinesterase inhibitor are also seen and may include tremors, incoordination, paresis, paralysis, and terminal respiratory paralysis. Note in anatoxin-a(s) toxicosis, retinal and brain cholinesterases are not inhibited, as it appears that the toxin cannot cross the blood brain barrier (BBB). The only centrally mediated signs are likely to be due to terminal hypoxia.
- Pigs and dogs are extremely sensitive to oral exposure. Ducks are of intermediate sensitivity. Cattle and lab rats are relatively resistant to orally administered anatoxin-a(s) containing algae, but these species are sensitive to parenterally administered lysed algae.

Lesions

- Algae-associated discoloration of hair and skin indicates exposure.
- Algae may or may not be evident in the gastrointestinal tract.
- Anatoxin-a toxicosis produces no lesions.
- Anatoxin-a(s) toxicosis causes diarrhea, salivation, excessive urination, and possibly a sticky mucoid ocular discharge, evidence of which may be found on examination of the animals prior to or at necropsy.

Diagnosis

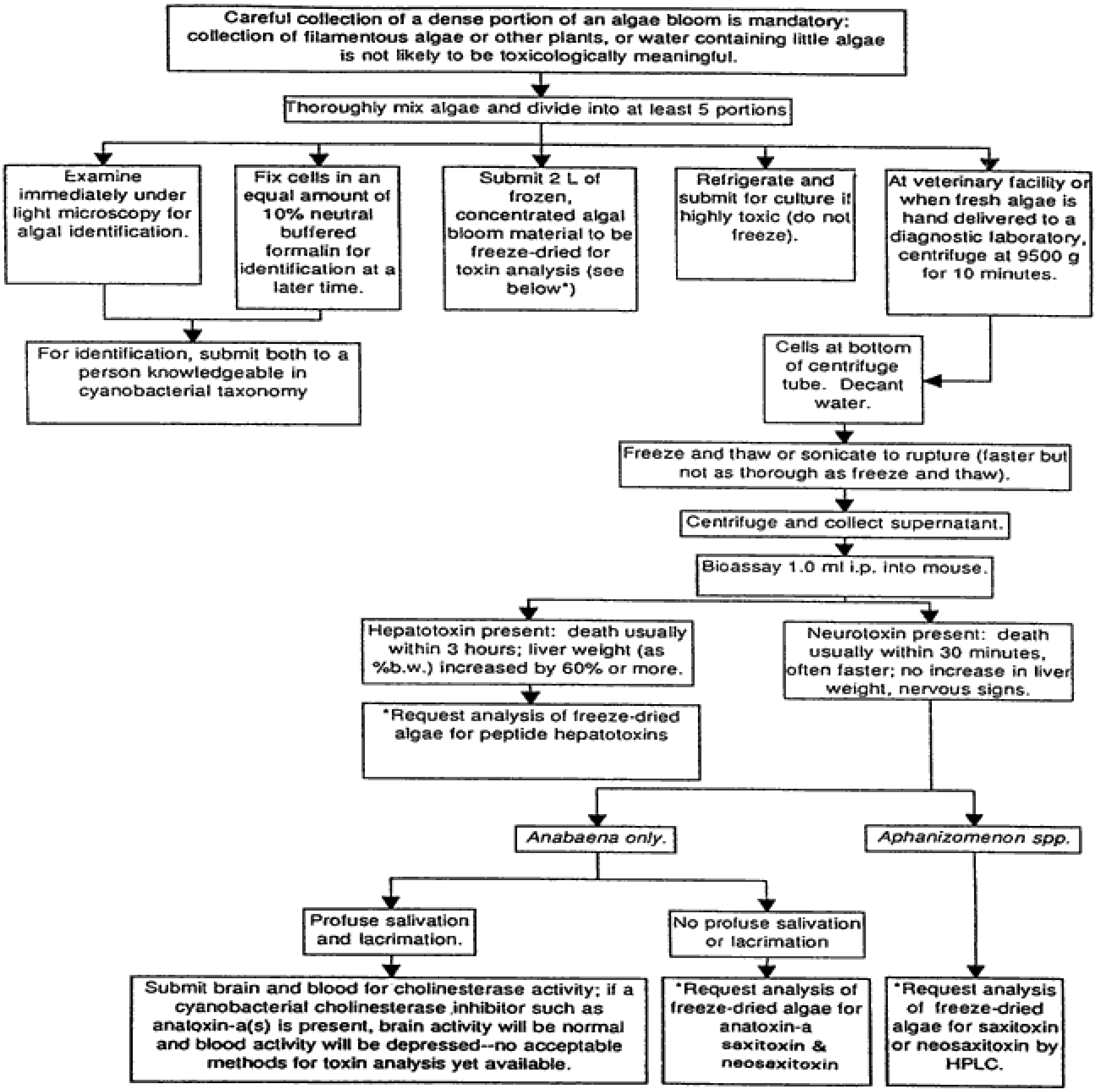
- The principle criteria for tentative diagnosis include ingestion of a significant amount of a blue-green algae and appropriate clinical signs.
- Initial microscopic examination of bloom material revealing the appropriate chains of algal cells increases the assurance of the diagnosis.
- In anatoxin-a(s) toxicosis, there are depressed blood, plasma, and (in lethal cases) skeletal muscle cholinesterase activities with normal retinal and brain cholinesterase activities.
- For lethally poisoned animals, a complete necropsy should be used to rule out other causes and, in the case of hepatotoxin, to reveal the appropriate gross and histologic lesions.
- The Illinois CVM toxicology laboratory can arrange for analysis of stomach contents and algal bloom material for the hepatotoxin and for anatoxin-a. At this time, there are no analytical methods available for anatoxin-a(s).
- Confirmation of algal species is also dependent upon further examination of the algae. Kits to obtain appropriate algal specimens may be obtained from Dr. Wayne Carmichael, Department of Biology, Wright State University, Dayton, Ohio. In cases of acute toxicosis, the specimens often can be collected and sent to Dr. Carmichael for organism culturing (small amount of "scum" added to bacterial transport media, refrigerated), organism identification (small amount of "scum" in an equivalent of 10% neutral buffered formalin), toxin analysis (2 L concentrated "scum", frozen), and when necessary, toxin bioassay using mice.

Treatment

- Avoid further exposure by fencing off contaminated ponds and lakes, as well as streams emanating from them. It has been theorized that, immediately after treatment with copper sulfate, an algal bloom may be of increased toxicity due to cell breakdown and a greater access to the toxin(s) present. This now seems unlikely in the case of the hepatotoxin but may be true for the neurotoxins.
- For apparent anatoxin-a poisoning, the rapidity of onset may make treatment impossible. If consumption has just occurred, measures to evacuate the gastrointestinal tract, bind the toxin (activated charcoal is likely to be benefit), and maintain respiration (artificial respiration) may be needed. Without additional therapy to remove the algae or bind the toxins, artificial respiration (for many hours) may not do anything more than prolong the onset of death. Whether the detoxification measure will be of benefit is not yet proven but seems plausible.
- For apparent anatoxin-a(s) toxicosis, atropine may be effective (take care using in horses to avoid gut stasis and associated colic, which can be severe). Employ measures to terminate toxin absorption as

described for anatoxin-a. Artificial respiration may also be of value, although the effects of the toxin are relatively persistent. There is no data to indicate a need for oxime therapy for anatoxin-a(s)-poisoned animals.

- For hepatotoxin poisoning, prognoses are poor in severely affected animals. Combatting shock and hemorrhage with fluids and blood are clearly indicated as is dextrose if hypoglycemic and measure to counteract hyperkalemia (if present), but severe liver damage may often preclude an uneventful recovery. Regeneration of hepatocytes in sublethal toxicosis has, however, been documented in mice.


Careful collection of a dense portion of an algae bloom is mandatory: collection of filamentous algae or other plants, or water containing little algae is not likely to be toxicologically meaningful.
Thoroughly mix algae and divide into at least 5 portions
Examine immediately under light microscopy for algal identification.
Fix cells in an equal amount of 10% neutral buffered formalin for identification at a later time.
Submit 2 L of frozen, concentrated algal bloom material to be freeze-dried for toxin analysis (see below*)
Refrigerate and submit for culture if highly toxic (do not freeze).
At veterinary facility or when fresh algae is hand delivered to a diagnostic laboratory, centrifuge at 9500 g for 10 minutes.
For identification, submit both to a person knowledgeable in cyanobacterial taxonomy
Cells at bottom of centrifuge tube. Decant water.
Freeze and thaw or sonicate to rupture (faster but not as thorough as freeze and thaw).
Centrifuge and collect supernatant.
Bioassay 1.0 ml i.p. into mouse.
Hepatotoxin present: death usually within 3 hours; liver weight (as %b.w.) increased by 60% or more.
Neurotoxin present: death usually within 30 minutes, often faster; no increase in liver weight, nervous signs.
*Request analysis of freeze-dried algae for peptide hepatotoxins
Anabaena only.
Aphanizomenon spp.
Profuse salivation and lacrimation.
No profuse salivation or lacrimation
Submit brain and blood for cholinesterase activity; if a cyanobacterial cholinesterase inhibitor such as anatoxin-a(s) is present, brain activity will be normal and blood activity will be depressed--no acceptable methods for toxin analysis yet available.
*Request analysis of freeze-dried algae for anatoxin-a & saxitoxin & neosaxitoxin
*Request analysis of freeze-dried algae for saxitoxin or neosaxitoxin by HPLC.

4.Toxicants with Nicotinic Effects

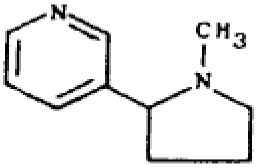
Nicotine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases,
All species, esp. dogs and other small companion animals	Minutes to 2 hours	Hours; often lethal	

			Voluntary Nerves as Well)

Source

- Alkaloid from *Nicotiana tabacum* (tobacco), 2 - 8% in leaves (dried).
- Nicotine sulfate.
    - 0.05 - 4.0% in dusts and sprays to control insects.
    - 40% in a concentrated solution (Black Leaf 40).
    - Also used in immobilizing agent (Cap-Chur-Sol) via projectile syringe (Cap-Chur Gun-dart); very narrrow margin of safety.
- Cigarettes-up to 20 mg of nicotine each; cigars up to 40 mg. Cigarette butts contain about 25% of the total nicotine content.
- A pack of cigarettes was reported to be lethal to a dog.
- Snuff contains from 4.6 - 15 mg of nicotine/1 gram moist material.
- Chewing tobacco: 2.5 - 8.0 mg nicotine/1 gram dry material.
- Nicotine gum (Nicorette ®) contains 2.0 mg of nicotine. Its bioavailability is reportedly comparatively low at only 15%.



Nicotine

Toxicity

- LD_{50} insects - 200 - 300 mg/kg.
- LD_{50} oral mouse 24 mg/kg; oral rat 55 mg/kg.
- Minimum LD canine and feline: approx. 20 - 100 mg total dose.
- Lethal dose equine 100 - 300 mg total dose.
- Lethal dose ovine 100 - 200 mg total dose.
- A total dose in humans of 40 mg has been lethal.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Poor absorption from the stomach. Absorbed from and also may cause some irritant effects on the mucous membranes of the mouth, pharynx, and esophagus. Alkalinization of the stomach enhances absorption.
- Potent emetic effect may limit intestinal absorption.
- Absorbed from the intestine, respiratory tract, intact skin.
- Nicotine from Nicorette® gum reported results in maximal blood concentrations of nicotine at 15 - 30 minutes after being chewed. The peak may be reached at a later time in dogs that may ingest it without chewing very much and that may also ingest wrappers that impede digestion.
- Undergoes metabolism in the liver, kidneys, and lungs.

Mechanism of Action

- Mimic of acetylcholine at sympathetic and parasympathetic ganglia, neuromuscular junctions of skeletal muscle and at some synapses in the CNS. Low doses cause depolarization and stimulation of receptors similar to acetylcholine. Higher doses cause stimulation followed by blockade at autonomic ganglia and myoneural junctions of skeletal muscle.
- Cardiovascular: stimulation of sympathetic ganglion and adrenal medulla leading to release of catecholamines.
- GI: parasympathetic stimulation leading to increased tone and motor activity.
- Death is a result of respiratory paralysis.

Signs

- Rapid onset (15 - 45 minutes after exposure) and progression of the syndrome (minutes to a few hours in most instances. Duration 1 - 2 hours following mild exposure to 24 hours following severe intoxication.
- Excitation, tachypnea, salivation, lacrimation, emesis, and diarrhea.
- Followed by: muscle weakness, twitching, depression, tachycardia, shallow, slow respiration, collapse, coma, cyanosis, cardiac arrest, death.

Lesions

Cyanosis, lesions possibly associated with an agonal death.

Diagnosis

- History of exposure to toxic amounts, signs and relative absence of lesions.
- Confirmation: Nicotine in urine, blood, liver, kidney or other tissues; or in gastrointestinal tract contents, vomitus, or lavage washings.

Treatment

- Poor prognosis with large doses.
- Sublethally dosed animals generally show some improvement within 3 hours or so.
- Dermal exposure-vigorously bathe with liquid dish detergent (or unmedicated shampoo: use thick rubber gloves to prevent human exposure; surgery gloves may not be an effective barrier to many different toxicants).
- Oral exposure: if thorough emesis has not occurred and if not contraindicated an emetic may be used. Alternatively, lavage or enterogastric lavage may be indicated.
- Activated charcoal should be left in the digestive tract. Repeated doses (up to 3) of a dilute slurry of activated charcoal may be of value at 2, 5, and 8 hours after the initial activated charcoal dose.
- Atropine may be used if parasympathetic effects are present-doses may be similar to those used for organophosphate toxicoses (work up to the dose however, starting with preanesthetic doses and repeating periodically until the appropriate response is achieved).
- Artificial respiration and oxygen as indicated. Fluid therapy if hypotension occurs.
- Nicotine toxicoses may be shortened by acidification of the urine which may promote urinary excretion. This must be reserved for animals which are not already acidotic as a result of respiratory impairment, cardiovascular dysfunction, exertion (tremors, etc.) or seizures.
- Control seizures if needed with diazepam or barbiturate.
- **Do not** administer antacids since nicotine is better absorbed from a more alkaline stomach.

Nicotiana spp. - Tobacco

N. tabacum - tobacco, burley tobacco
N. attenuata - coyote tobacco, wild tobacco
N. trigonella - desert tobacco
N. glauca - tree tobacco
N. trigonophylla

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Herbivores, swine, dogs, birds	Minutes to hours	Hours; potentially lethal; teratogenic	

Family - Solanaceae.

Habitat

- *N. attenuata* - Wyoming and Washington, to California and Mexico, especially S.W. USA, dry sandy soils, along dry stream beds.
- *N. trigonella* - Southern Nevada, Utah, and Colorado to California; Western Texas, Mexico and Central America, arid or semi-arid valleys.
- *N. glauca* - Southern USA, Texas to California, Along the Rio Grande, Mexico, Argentina, Hawaii, waste areas below 3000 ft.
- *N. tabacum* - USA, southeastern, and eastern states, cultivated fields.

Description

Rank, acrid herbs, annual or perennial, shrub or small tree, 1 - 4 feet tall. Sticky haired stem, with alternate leaves. Lower leaves are oblong to egg-shaped but upper leaves are more lanceolate with sharp or blunt tips. Leaves are simple and opposite, usually have smooth edges, broad, hairy, and sticky. Flowers are terminal or branched, 5-lobed, tubular and about 2 in. long, greenish-white, yellowish or lavender. Fruit is a 2 celled capsule with many seeds.

Toxic Principle

The alkaloids nicotine and teratogenic agents including anabasine, anatabine, and anabaseine. Carcinogenic polycyclic aromatic hydrocarbons such as benzo(a)pyrene are produced during combustion.

Absorption, Distribution, Metabolism and Excretion (ADME)

Nicotine in pesticides is rapidly absorbed from gastrointestinal tract and skin. Nicotine and other alkaloids, when present in tobacco, may be absorbed more slowly.

Toxicity

- Tobacco plants are unpalatable and animals generally avoid consumption.
- The entire plant is poisonous, foliage contains a high content of nicotine; tops are most toxic.
- Because tobacco stalks are high in nitrogen, they are often returned to the soil to increase fertility and may poison foraging animals.
- Small animals ingest tobacco, which causes centrally mediated vomiting, therefore, tobacco poisoning is infrequently fatal.
- Horses have died as a result of eating leaves of harvested tobacco, when kept overnight in a tobacco barn. The minimum toxic dose is 0.68% of body weight.
- Children have been poisoned by sucking the flower; leaves used in salad have proven fatal.
- Fatalities are common in cattle. The minimum lethal dose of *N. trigonophylla* is approximately 2% of body weight on a green-weight basis.
- Estimated LD_{50} in sheep 2.3 - 3.4 mg/kg of anabasine. *N. glauca* contains 0.45 - 1.14 mg of anabasine/gram of dry weight. Moderate to severe clinical signs occurred at levels that provided 0.56 - 0.78 mg anabasine/kg body weight. Gilts had moderate to severe signs when dosed at levels that provided 0.23 - 0.84 mg anabasine/kg body weight. At the upper dose levels, piglets were deformed at an incidence of about 50%.
- In sheep, the minimum toxic dose is 1.5% of the body weight and the lethal dose is 3.25% of BW.

Susceptible Species

- Cattle, swine, sheep, horses, and birds have been reportedly poisoned by ingestion of tobacco plants.
- Small animals (dogs, cats) have developed toxicosis following ingestion of tobacco containing products.

Mechanism of Action

- Initially stimulate ganglia of sympathetic and parasympathetic nervous systems by direct action on ganglion cholinergic receptors.
- Followed by ganglionic blockade due to persistent depolarization.
- CNS initially stimulated (tremors, convulsion) followed by depression.

- Death due to respriatory failure from neuromuscular blockade.

Signs

- Signs become apparent from 15 minutes up to several hours after exposure.
- Staring into space, wretching, vomiting, salivation, abdominal cramps, bloat, frequent urination, colic, diarrhea.
- Muscular weakness, staggering, tendency to fall on forelimbs, lameness, trembling, shivering, spasms, muscle tremors, 3rd eyelids drawn, blindness, dullness, stupor.
- Irregular, weak pulse, or violent palpitation of the heart.
- Prostration, opisthotonus, diaphragmatic spasms.
- Elevated body temperature, but extremities feel cold.
- Dyspnea, respiratory paralysis and death.
- In swine, the primary problem is teratogenesis. Pregnant sows eating tobacco stalks may give birth to pigs with arthrogryposis. Arthrogryposis is aflexion, anterior or posterior of limbs with medial deviation of limbs. Day 35 seems to be the end of the dangerous period. As an apparent result of the limb deformity, prolongation of parturition kills many pigs from neonatal asphyxiation. Sows may not show signs of toxicosis before giving birth to malformed pigs.
- Sometimes over 1/2 the pigs on a farm are born abnormal. Unable to nurse normally, piglets may die from hypoglycemia.
    - No effect on fertility of sows.
    - No increase in abortions.
- Teratogenic effects noted in offspring from sheep feeding on *N. glauca* during the 30 - 60th day of gestation. Teratogenic effects included carpal flexure, lordosis, facial deformities, and cleft palate.

Lesions

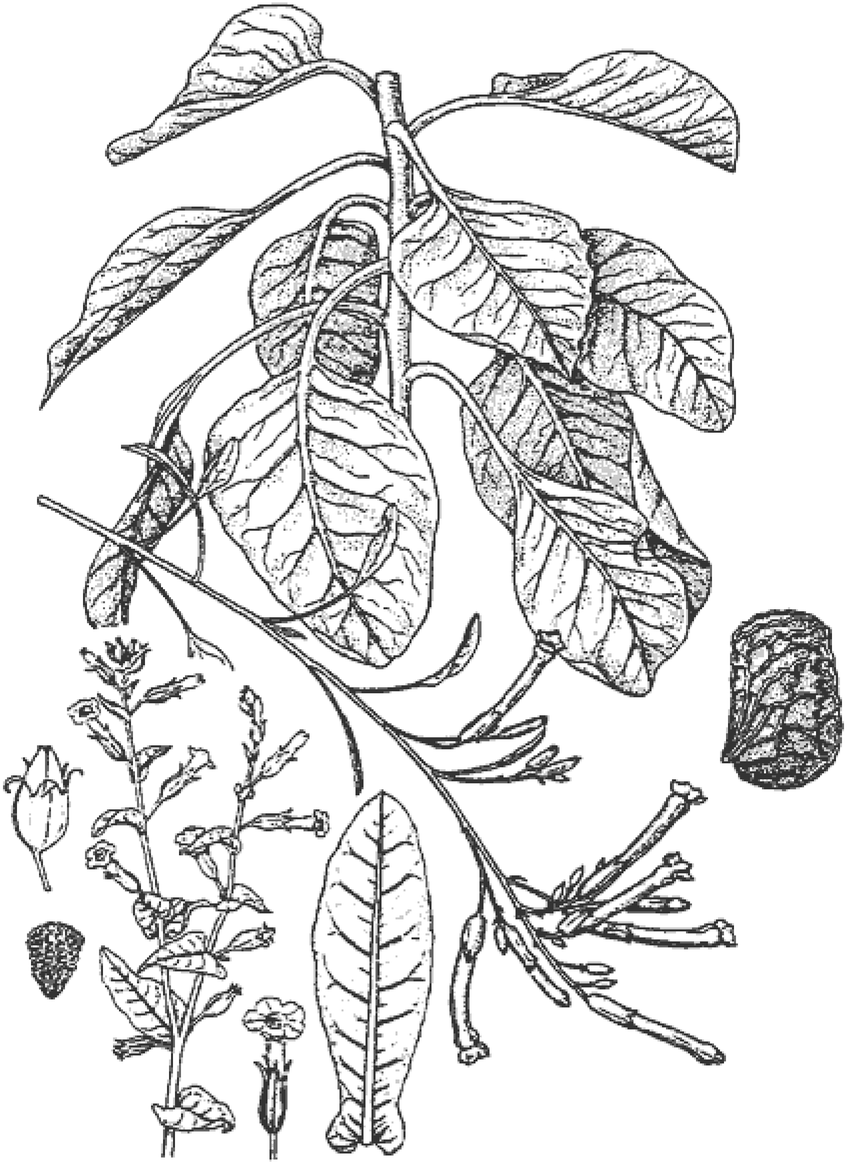
- There may be ingesta in the trachea or lungs from aspiration. In ruminants, the abomasum may be congested, and there may be engorgement of subcutaneous blood vessels. Obviously, these lesions are non-specific.
- Arthrogryposis: Affects primarily the appendicular skeleton, but the spinal column and mandible have been affected. There may also be clubbing of one or more feet and acute kyphosis (humpback) and brachygnathia. Affected bones become thickened, curved, twisted, or shortened, and there may be malallignment of joints.

Treatment

- Emetic if no contraindications exist.
- Lavage followed by administration of activated charcoal and saline cathartic.
- Artificial respiration and oxygen therapy may be required.

Prevention

Supplemental feed, when forage is scarce will reduce the likelihood of toxicosis. Pregnant swine should not be pastured on tobacco stalks/roots.



Tree and Desert Tobaccos - The large oval leaves of tree tobacco are shown above, the flowers in the center, and the seed (enlarged) in the right center. The flowers, leaves, seed (enlarged), and seed pods of desert tobacco are at lower left.

Lobelia

Lobelia inflata - Indian tobacco, lobelia, eye bright, asthma weed, gag root, puke weed, wild tobacco
L. siphilitica - Great blue lobelia, great lobelia, high belia, Louisiana belia, Blue cardinal flower
L. dortmanna - Water lobelia
L. cardinalis - Cardinal flower, hog physic, Indian pink, red lobelia, scarlet lobelia
L. berlandieri - Berlandier lobelia

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Indian Tobacco (*Lobelia*)	Sheep, cattle, goats	Minutes to hours	Days to weeks; potentially lethal	
Cardinal flower (*Lobelia*)	Sheep, cattle, goats	Minutes to hours	Days to weeks; potentially lethal	

Giant lobelia (*Lobelia*)	Sheep, cattle, goats	Minutes to hours	Days to weeks; potentially lethal	

Habitat

- *L. inflata*.
    - Eastern Canada to Georgia; less common in areas westward to Nebraska and Arkansas. Meadows, pastures and cultivated fields.
- *L. siphilitica*.
    - Eastern USA and north central states. Near springs and swampy ground or wet pastures.
- *L. dortmanna*.
    - Northern USA, Canada and Europe. In shallow water or immersed borders of ponds, lakes and streams.
- *L. cardinalis*.
    - Quebec to Minnesota, southward to the southeast corner of Colorado, and east to Texas and Florida (includes Midwest).
- *L. berlandieri*.
    - Texas gulf coast (Hidalgo, Cameron, and Willacy counties) in moist habitats; Mexico.

Description

- *L. inflata*
    - Erect, 12 - 32 inches tall, with milky sap. The stem is densely branched, and hairy. Leaves are alternate, ovate to oblong, toothed. Flowers are in loose racemes, tubular, 5 lobed, with 5 stamens, and pale blue in color. The fruit is 2 celled, opens at the apex and contains many seeds.
- *L. siphilitica*.
    - Erect (3.3 feet tall) perennial, somewhat hairy stem that is stout and mostly simple. Leaves are alternate and ovate to lanceolate, thin and pointed at both ends, 2 - 6 inches long and irregularly serrated. Flowers are leafy, 3/4 inches long and bright blue to rarely white.
- *L. dortmanna*.
    - Very smooth perennial, with a simple stem. Leaves are clustered at the base, linear and hollow. Few flowers are present in loose racemes, white or pale blue.
- *L. berlandieri*.
    - Annual with erect or decumbent stems that are smooth and glabrous or sparsely hairy near the base. Stems usually bear 12 or fewer leaves which become papery when dry. Lower leaves often crowded into a rosette at the base of the plant leaves.

Toxic Principle

- Alkaloids lobeline and lobelidine. Altogether there are at least 14 pyridine alkaloids which are similar to nicotine.
- Lobeline stimulates carotid body chemoreceptor, interacts with nicotinic acetylcholine receptors, and is a respiratory stimulant.
- *L. berlandieri* may contain N-methyl piperidine.

Toxicity

- Entire plant is toxic. Dermatitis may result in man from contact with the leaves. Overdoses from home medicines made from this plant (dried leaves, tops) have proven fatal. Toxic quantities are not commonly ingested.
- Roots and seed capsule considered most toxic. Alkaloid content of plant varies from 0.13 - 0.63%. Highest alkaloid concentrations just before and after plant flowers. Flower stalks can have 0.9 - 1.1% lobeline.

Susceptible Species

- Include sheep, cattle and goats (and probably all other warm-blooded species). Signs include sluggishness, salivation, diarrhea, anorexia, and nasal secretion. Hemorrhage, ulceration about the mouth and coma. Dilation of pupils.

- *L. berlandieri* (in cattle and goats).
- Apparent outbreaks of *L. berlandieri* toxicosis have affected up to 1500 cattle and 500 goats.

Signs

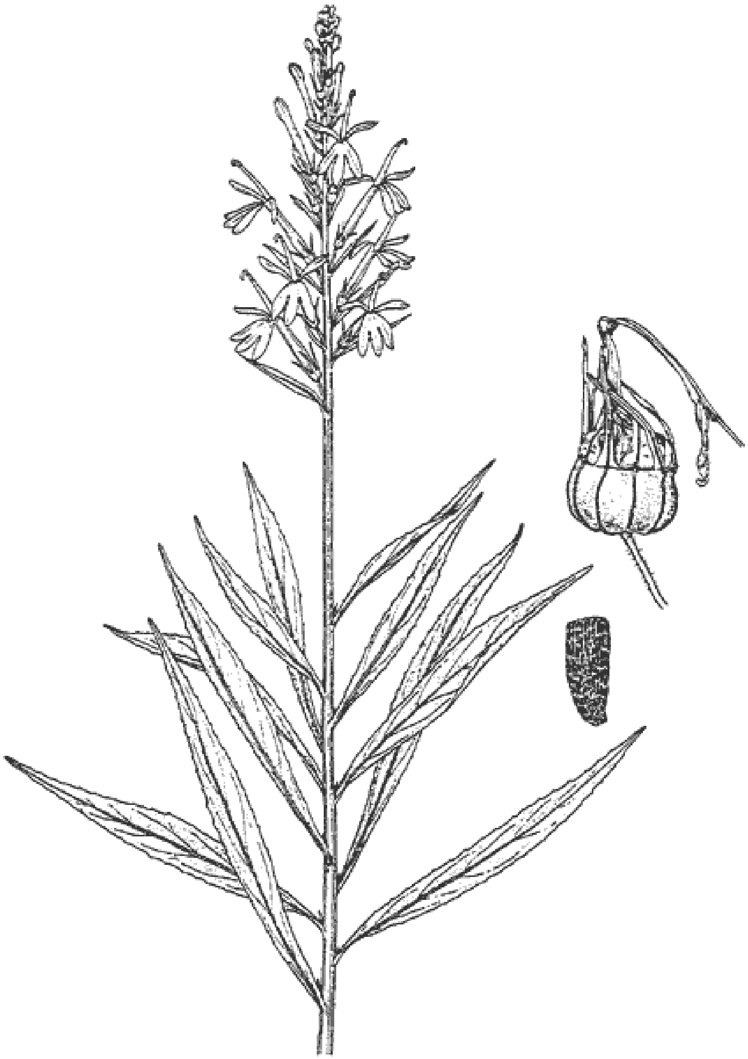
- Lobeline (general).
- In humans: nausea, vomiting, perspiration, exhaustion, weakness, prostration, mydriasis, pain, paralysis, depressed body temperature, rapid feeble pulse, stupor, tremors, coma, convulsions, and death.
- *L. berlandieri* in cattle: causes profuse salivation, dilation of pupils, atrophy of leg muscles, and extreme narcosis but animals retain normal appetites.

Lesions (All Species of *Lobelia*)

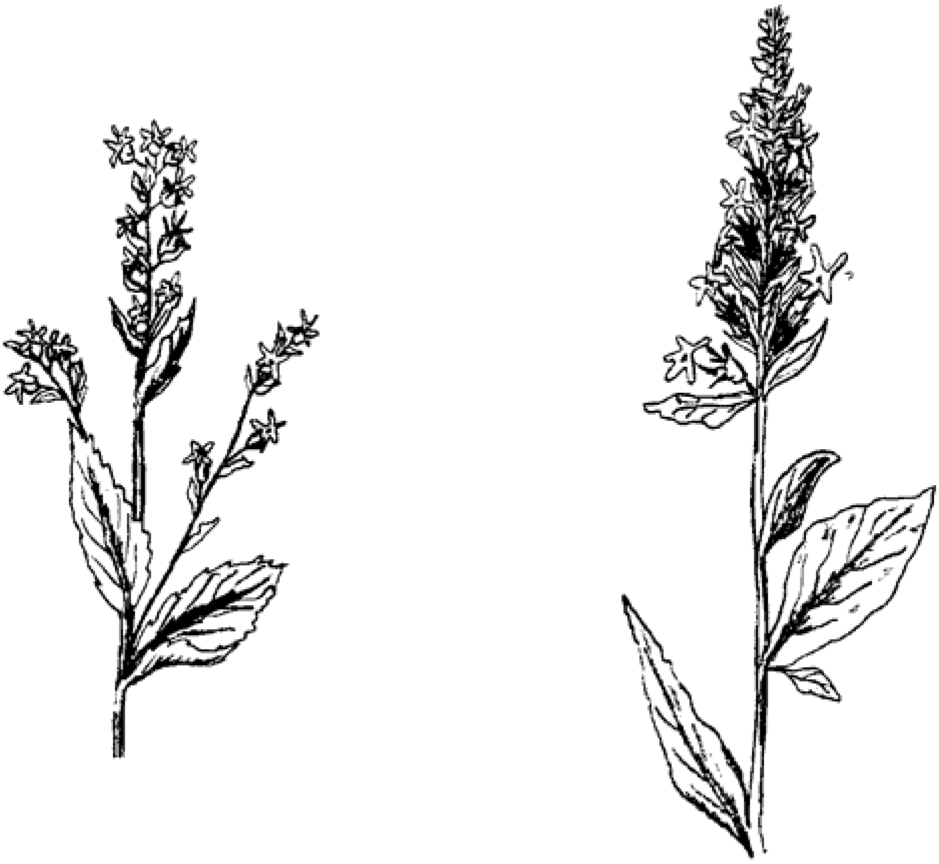
- Nonspecific. Widely distributed hemorrhage may be seen but mild gastroenteritis is more likely to be observed.
- *L. berlandieri* subcutaneous hemorrhage, subdural edema, and congestion of brain.

Treatment

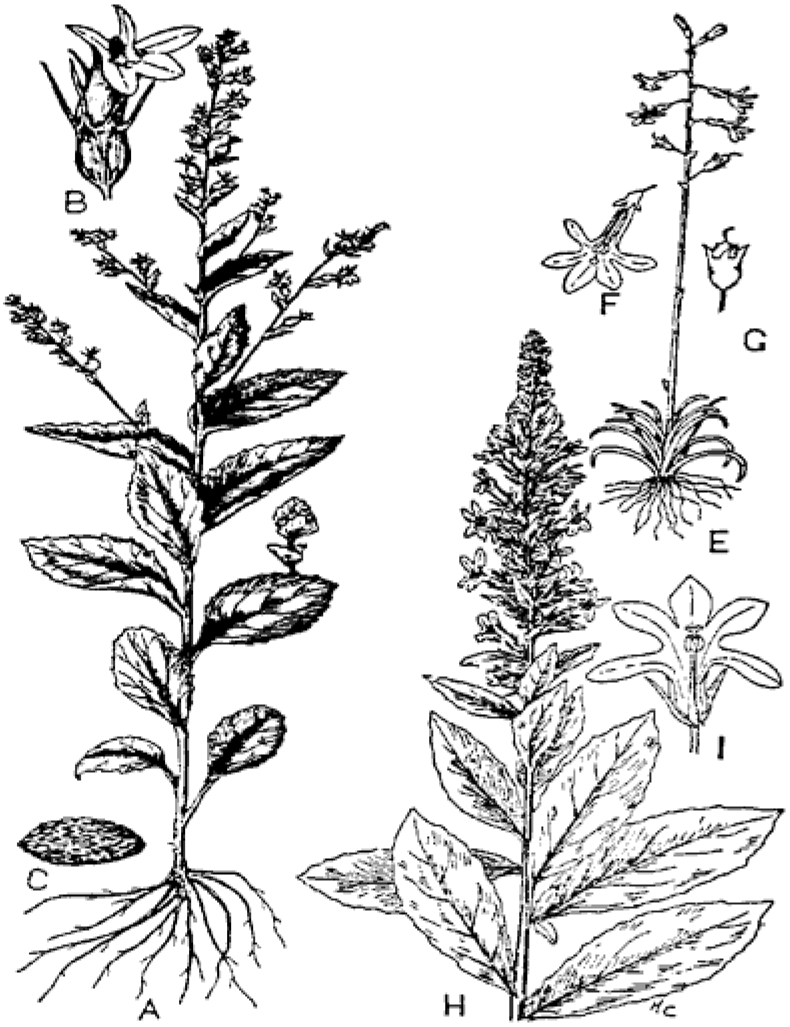
If not contraindicated, induce emesis. Otherwise consider lavage, activated charcoal, saline cathartic. Provide respiratory support if needed. Treat any seizures with diazepam.



Cardinal Flower - Distinctive red 2-lipped tubular flowers and lance-shaped leaves are characteristic of this tall colorful herb. At right center the enlarged seed capsule and pitted seed are shown.



Lobelia inflata and ***Lobelia siphilitica.***



***Lobelia inflata*, Indian tobacco.** - **A**, plant showing general habit; x 1/3. **B**, flower; x 2. **C**, seed; x 18. *Lobelia dortmanna*. Water lobelia. **E**, plant; x 1/3. **F**, flower; x 1/2. **G**, capsule; x 1/3. *Lobelia siphilitica*. Great lobelia. **H**, flowering shoot; x 1/3. **I**, flower; x 1/2.

Conium - Poison Hemlock

Conium maculatum - Poison hemlock, European hemlock, spotted hemlock

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Cattle, swine, poultry, horses, sheep	Minutes to hours	Hours; potentially lethal; teratogenic	

Description

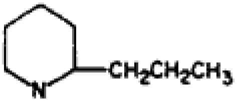
- Coarse, erect, biennial herb, 1 - 3 m tall.
- Smooth, purple spotted, hollow stems. Purple spots more prominent near base.
- Parsley-like alternate, compoundly dissected leaves.
- Flowers are small, white, and in umbrella-shaped clusters. Terminal umbels of flowers 4 - 6 cm across.
- Leaves smell like parsley when crushed. Crushed stems, leaves, and roots may have pungent odor.
- Nauseating taste.

Habitat

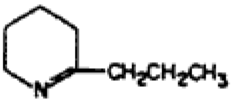
- Fertile soils and fields, fencerows, roadsides, meadows, along streams.
- Native in Europe but now in most of USA, common in midwest among other areas.

Toxic Principles

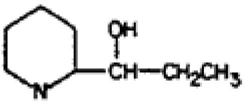
- Piperidine (nicotinic) alkaloids including γ coniceine, coniine, N-methyl coniine, conhydrine, and pseudoconhydrine.



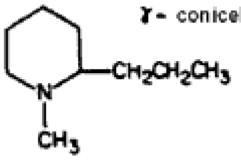
Coniine



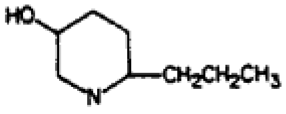
γ- coniceine



Conhydrine



N- methylconiine



Pseudoconhydrine

- Alkaloid content variable with stage of development and stage of reproduction of plant.
- First year plant low alkaloid content. Plants in second year have alkaloid contents of approximately 1% in all plant parts.
- Alkaloid content is somewhat higher after sunny weather, as compared to rainy weather.
- Vegetative stage-Early, primarily γ coniceine.
- Coniine (2-propylpiperidine) and N-methyl coniine progressively increase in flowers and fruits while γ coniceine decreases during plant development.
- Highest concentration of alkaloids is in seeds which can contaminate poultry and swine cereal grains.
- γ coniceine and coniine are the primary teratogenic alkaloids of *Conium*.

Toxicity

- Tea made from poison hemlock reportedly killed Socrates.
- Cows displayed severe clinical signs at 3.3 mg coniine/kg bw.
- Mares have severe signs at 15.5 mg/kg and ewes appeared most resistant requiring 44.0 mg/kg of coniine before severe clinical signs developed. At these levels no teratogenic effects were noted in offspring from pregnant mares or ewes.
- Fatal poisoning in swine with 9 g/kg bw of fresh immature plant.
- Similar range of toxicity seen with parenterally administered alkaloid extracts.

Susceptible Species

- Spontaneous (natural) exposure has caused poisoning in cattle, swine, elk, and poultry.
- Toxicosis experimentally reproduced in sheep and horses as well.

Poisoning

Eaten mostly in early growing season.

Mechanism of Action

- Coniine stimulates and then depresses autonomic ganglia and motor end plates in skeletal muscle.
- Large doses can cause neuromuscular block.
- Effects are similar to nicotine but have greater CNS and neuromuscular paralytic effects.

Signs

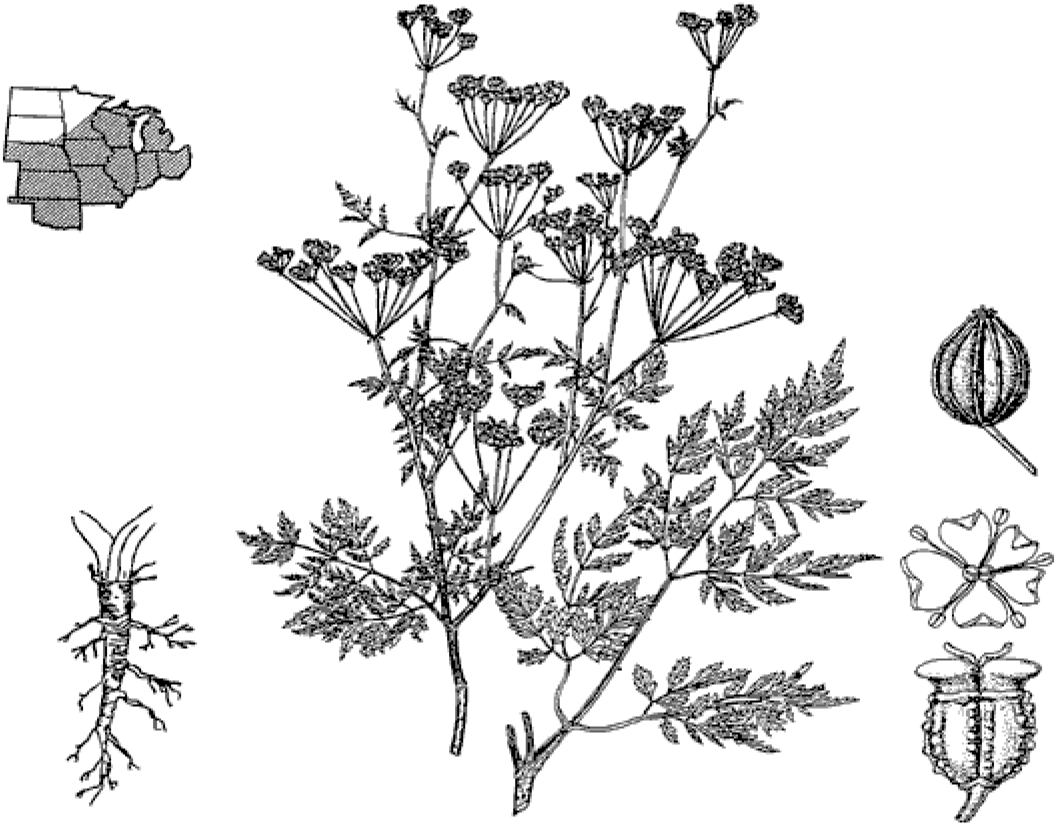
- Systemic effects.
    - Initially nicitating membranes of eyes closed, producing temporary (15 - 30 minutes) blindness in affected sows. Mydriasis.
    - Muscle tremors, ataxia, muscle weakness. "Nervousness" first followed by severe depression.
    - Frequent urination, defecation.
    - Hypersalivation.
    - Abdominal pain.
    - Incoordination, recumbency.
    - Breathing ceases before cardiac arrest. Death due to respriatory paralysis.
- Teratogenic effects. Deformities in joints are prominent.
    - Occur in (at least) calves and piglets and may include:
        - Crooked legs (crooked calf disease, arthrogryposis).
        - Cleft palate.
        - Kinked tails.
    - Arthrogrypotic skeletal malformations occur in calves when poison hemlock is ingested by pregnant cows between days 40 through 70 of gestation. Similar skeletal lesions occur in swine between days 42 through 61 of gestation.
    - Cleft palates can be induced in piglets if pregnant gilts ingest poison hemlock between days 30 through 45 of gestation.

Diagnosis

- Appropriate exposural history and clinical signs.
- "Mousy" odor to urine and expired air.
- Differential diagnosis for teratogenic effects include lupine species, *Nicotiana* sp., and poison hemlock.

Treatment

- Rapid onset-fairly rapid recovery.
- Activated charcoal, appropriate steps to evacuate the GI tract.
- Saline cathartic.
- Support respiration.
- Atropine may be given if severe parasympathetic signs are present (cautious in horse: avoid stasis of the gut!). If gastrointestinal effects not severe, it may be best to avoid atropine in any species because of atropine-induced delayed intestinal transit which may increase absorption.
- Gastric or rumen lavage or rumenotomy may be of benefit if recently ingested. However, the stress involved may exacerbate clinical signs of the toxicosis.



Poison-Hemlock - Note the large pinnately divided leaves, the flat-topped clusters of flowers and fruits, the female flower (enlarged, lower right) with enlarged male flower above, and ribbed fruit capsule (enlarged, right center) of this poisonous herb.

Lupinus - Lupine or Bluebonnet

Lupinus leucophyllus - Velvet lupine, wooly-leaved lupine
Lupinus leucopsis - Big bend lupine (may be the same plant as L. sericens listed below)
Lupinus argenteus - Silvery lupine
Lupinus sericens - Silky lupine
Lupinus cyaneus
Lupinus onustus - Plumas lupine
Lupinus laxiflorus - Douglas spurred lupine, loose flower lupine
Lupinus alpestris
Lupinus caudatus - Kellogg's spurred lupine
Lupinus greenei
Lupinus pusillus - Low lupine
Lupinus polyphyllus - Washington lupine

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Sheep, cattle, and other herbivores	1 - 24 hours	Hours to days; potentially lethal; teratogenic	

Several other species also may be toxic including garden lupines planted in the midwest and east which may be responsible for rare toxicoses in children or small animals.

Habitat

- Approximately 100 species of lupine are present in the USA and Canada. Most are present in states and provinces from the Rocky Mountains westward.

Description

- Range species are mostly low, perennial shrubs; with alternate leaves which are palmately compound; with 5 - 17 leaflets, most leaflets are oblanceolate. Some *Lupinus* spp. are annuals.
- Flowers are terminal, often showy, blue, white, red or yellow with 10 stamens, and filaments are united in a single tubular structure; anthers are free, and alternating long and short.
- Fruit is a several-seeded, flattened legume pod.
- Begin to grow in early spring, flower in June, and form pods and seeds in late summer (July-August).

Toxic Principle

- More than a dozen quinolizidine alkaloids, but some piperidine alkaloids and other types of alkaloids have also been isolated from species of *Lupinus*. These alkaloids are largely nicotinic in effect. The nitrogen oxides of some of these bases have also been detected in some lupines.
- The alkaloids are present in the foliage but the greatest concentration is in the seeds.
- Anagyrine is a teratogenic alkaloid in *L. caudatus* that reportedly affects cattle but not sheep.

Conditions of Poisonings

- Cause more deaths than any other single plant in Montana, Idaho and Utah.
- Species and taxonomic differentiations between species are insufficiently characterized.
- Different lupines produce varying syndromes in a given species of livestock. Seasonal variation in toxicity in a given species of lupine exist and many species are acceptable forage under range conditions.
- Plants which are in the preflowering stage of maturity are unlikely to be hazardous, under normal range circumstances, except in the case of *L. leucophyllus* which may cause toxicosis as a result of consumption of young plants. Alkaloids are not lost upon drying. Range hay may be highly toxic if the seeds are retained; this occurs when the majority of the pods are immature; mature pods open when drying and the seeds are dropped as the hay is handled. For many lupines, the time and degree of seeding varies from year to year.
- Most losses occur under conditions in which animals consume large amounts of pods in a brief period, such as when they are being driven through an area of heavy lupine growth, unloading animals into such an area, trailing animals through an area where the grass is covered by snow but the lupine is not or when feeding podded lupine hay, which is apparently palatable.
- Most serious poisoning, therefore occur in the fall; lupine remains green after other forage has dried.

Toxicity

- Seeds alone are toxic to sheep at 0.25 - 1.5% of their body weight.
- Adverse effects in sheep occur when ingested 60 - 125 grams of lupine daily for 3 - 4 days.
- 0.5 - 0.75 kg of lupine can induce adverse effects in cattle.
- *L. laxiflorus* is more toxic to cattle, less toxic to sheep.

Susceptible Species

- Several outbreaks involving the loss of over 1000 sheep are on record.
- If other forage is available, sheep, the most commonly affected species, will avoid lupine.
- Goats, swine and deer have also been poisoned.
- Poisoning is rare in cattle and horses, because they usually do not readily consume the pods.

Signs

- Characteristic labored breathing (snoring) in sheep, with depression, salivation, ataxia, clonic spasms, head pressing tremors, seizures and coma, and frequently death. Death may be preceded only by

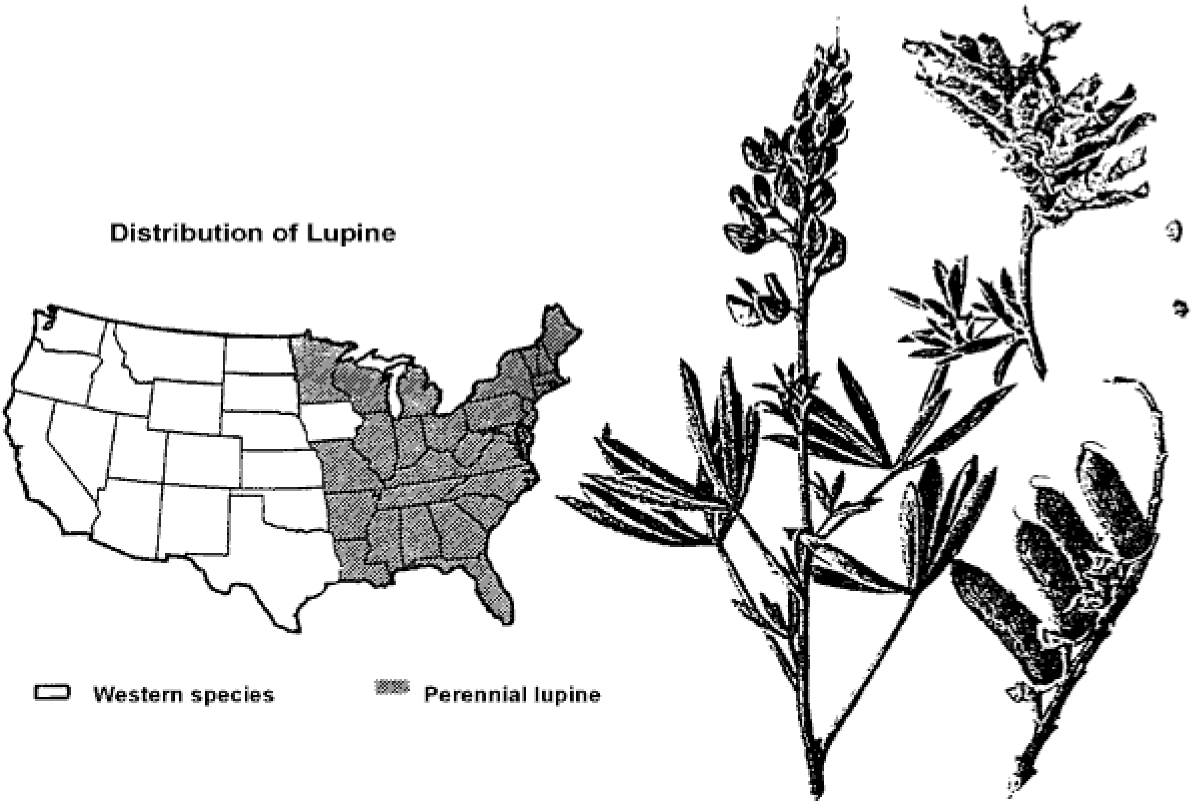
coma and no other signs (no struggling) or alternatively, preceded by violent attacks on other animals or objects.
- Signs may appear as early as one hour after ingestion or as late as 24 hours after consumption. Death may occur within one day or occur several days later and is a result of respiratory paralysis.
- Cattle under range conditions rarely display clinical signs.

Teratogenesis

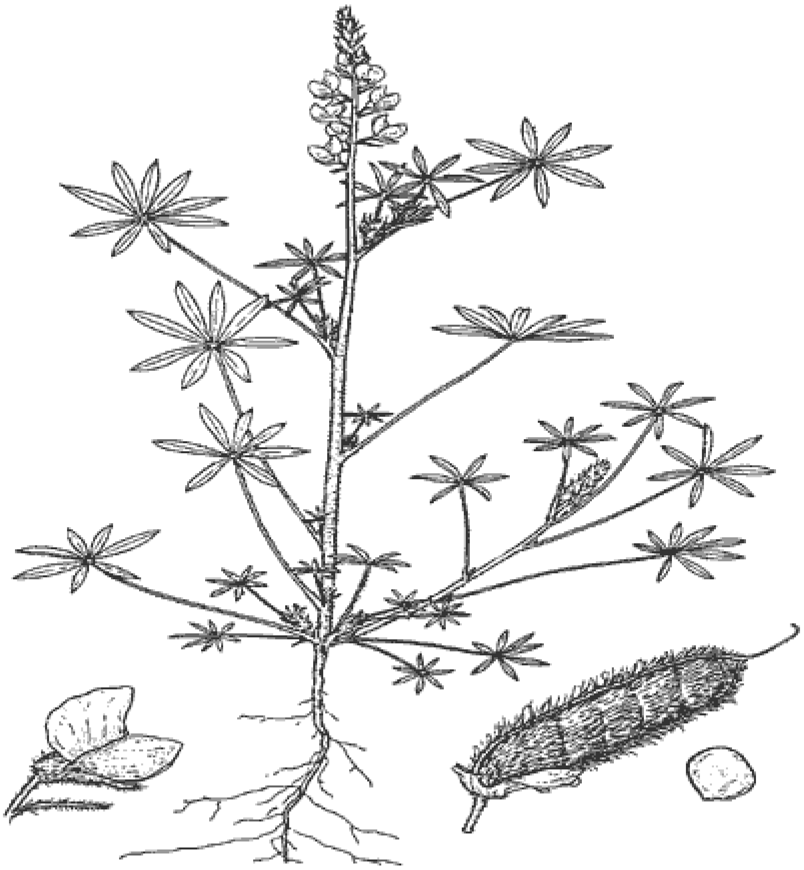
- Lupine ingestion is one cause of crooked calf disease which occurs in South Dakota, Nebraska and west to the Pacific, north to Canada. Incidence of crooked calves is highly variable geographically and from year to year within a given herd. Three to 35% of a given calf crop may be affected. Affected, malformed calves are usually born alive at full term and lesions include misaligned joints and twisted bones (arthrogryposis). In mild cases, deformity is confined to a mild bowing of the forelegs. In severe case, the forelegs are twisted and held in a flexed position.
- The neck and back may also be involved and rarely the rear legs.
- A cleft palate is sometimes present.
- No particular breed predilection or genetic pattern has been found.
- Under some circumstances, it is always associated with early calves and may ther efore be controlled by delayed breeding. The dangerous period of exposure during pregnancy is during days 40 - 70 of gestation. Slight to moderate deformities can occur from ingestion of lupines before and after this stage of gestation (30 - 100 days).
- The crooked calf syndrome has been reproduced by the experimental feeding of the alkaloid, anagyrine (at 30 mg/kg), the most teratogenic alkaloid of lupine.

Note

- European lupines differ in that they may also be hepatotoxic.
- Lupinosis of Australia is related to a hepatotoxin and is another entity, not to be confused with lupine poisoning in the USA.



Lupine (*Lupinus sericeus*) - All the species of Lupine are supposed to be poisonous, and are the cause of the larger part of the heavy losses of sheep during the late summer and fall months. Sheep are most likely to be poisoned by eating the pods and seeds.



Few-Flowered Lupine (*Lupinus sparsiflorus*) - Note the digitately divided leaves, the hairy foliage, the pea-shaped flower (lower left), and the flattened hairy seed pod and seed (enlarged, lower right) of this unusual plant.

Sophora - Mescal Beans

Sophora secundiflora - Mescal bean, burn bean, carol bean, red bean,and frijolillo. Sometimes called Texas mountain laurel (do not confuse with *Kalmia*, a more well-known mountain laurel)
***Sophora nuttalliana* (formerly *Sophora sericea*)** - Silky sophora
Sophora stenophylla
Sophora tomentosa - Necklacepod sophora, silver bush
Sophora japonica

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
(See Toxicants with Mixed Effects on the Central Nervous System)			

Family - Leguminosae (Pulse or Bean Family)

Description

- *S. secundiflora*.
    - Woody evergreen shrub or small tree (3 - 10 meters tall) in the pea family. Leaves are alternate, pinnately divided into 5 - 13 oblong leaflets. Leaflets have silky hairs on the underside and a shiny yellow-green surface above. Pea-like flowers are violet-blue, fragrant and grow in dense terminal clusters up to 4 inches (10 cm) long. One to 8 seeds are bright red and 1/2 inch (1.25 cm) in diameter in a woody pod, 1 - 7 inches long, just over 1/2 inch (1.25 cm) in diameter.

- *S. nuttalliana*
    - Plant is erect, 4 - 12 inches (10 - 30 cm) high. Stem is silky, woody at base. Leaves are alternate, pinnately compound; 7 - 25 hairy, oblong leaflets 0.5 - 5.0 inches (1.25 - 13 cm) long. Flowers are white. Fruit is a few-seeded, hairy, leathery pod 0.8 - 2.0 inches (2 - 5 cm) long.
- *S. tomentosa*.
    - Shrub, numerous branches with compound leaves. Flowers grow in racene and are bright yellow. Pea-like yellow seeds contained in pods.

Habitat

- Limestone hills, rock ledges, and canyons.
- *S. secundiflora*
    - Plants are native to southwestern Texas, southern New Mexico, and northern Mexico, and cultivated as showy ornamentals elsewhere in the Southwest. Plants grow best on limestone soils: range, hills, canyons.
- *S. nuttalliana*
    - Nebraska and Kansas to Texas and Arizona: prairies and Great Plains.
- *S. tomentosa*.
    - Florida, Bermuda, West Indies.

Additional Sources

- The seeds (mescal beans) were once used in medicine as a narcotic and hallucinogenic drug by Indians of Mexico and the Southwest. The drug produces intoxication characterized by excitement and delirium followed by deep sleep lasting a few days. Its use is no longer common (1990s).
- Mescal beans have been used extensively to make necklaces. Chewing the necklace beans can cause poisoning.

Toxic Principles

- The entire plant, especially the seed, is poisonous. These plants contain quinolizidine alkaloids.
- *S. japonica*.
    - Contains the nicotinic cytisine, the cardiotoxic and myotoxic lupanine, and the cardiotoxic and potential neurodepressant matrine, as well as lectins similar to compounds produced in the bark of black locust (*Robinia pseudoacacia*).
- *Sophora* is **not** the source of the hallucinogenic drug mescaline, which comes from the "mescal buttons" of peyote (*Lophophora williamsii*), and which also is produced synthetically.

Toxicity

- The LD_{50} for seed pods of some *Sophora* spp. in large animals is reported to be 0.5 g/kg. Toxin(s) may be somewhat cumulative.
- One thoroughly chewed seed is sufficient to cause the death of a child, but the hard unbroken whole seeds may pass through the digestive tract without harm. Mature foliage is more toxic to livestock than immature and may be harmful to humans if eaten or used to make tea.
- Several other southwestern species of *Sophora* also contain toxic alkaloids but are apparently less toxic than mescal bean.
- Suspected teratogen. In a pilot study by Keeler, *S. stenophylla* was teratogenic.

Susceptible Species

Cattle, sheep, goats, and man. Poisonings in small animals possible. Cattle may be most often poisoned.

Signs (*S. secundiflora*)

- Mucous membrane irritation, salivation.
- Nervousness, violent tremors, exercise-induced rigidity of rear legs, tremors, especially over shoulders and rump.

- Nausea, vomiting, diarrhea, excitement, delirium, hallucinations, paralysis, coma, and death due to respiratory paralysis. Nonlethal doses may cause a deep sleep that lasts for 2 - 3 days.
- Sheep usually recover after a time; cattle often die: cattle are more susceptible than sheep or goats.

Lesions

- None reported apart from teratogenic effects.
- Teratogenesis (arthrogryposis or contacted tendons) is believed to be associated with some species of *Sophora*.

Treatment

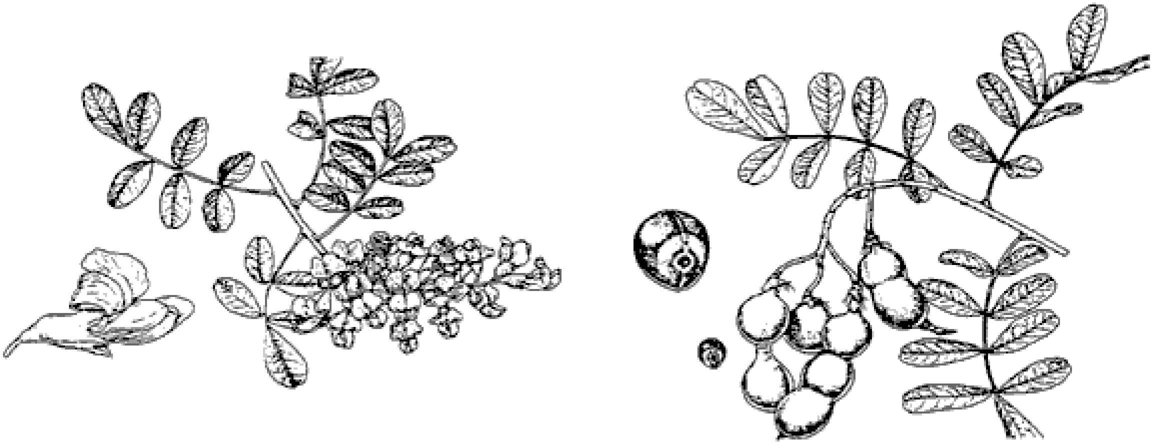
- Activated charcoal and cathartic.
- Treat as for nicotine toxicosis. Seizure control, correct hypotension (i.e., fluids), atropine for parasympathetic signs, e.g., bradycardia.

Prevention

Supplemental feeding when other forage is scarce.

Note

Don't confuse *S. secundiflora* (Texas mountain laurel) with *Kalmia* spp., the much more commonly encountered (in appropriate areas of the country) plant known as mountain laurel, which causes an entirely unrelated (andromedotoxin-mediated) syndrome.



***Sophora secundiflora* (mescal bean)** - The plant has pinnately divided leaves, clusters of purplish pea-like flowers (enlarged, left center), constricted pods (lower center), and bright red seeds (enlarged, lower left).

Gymnocladus dioica - Kentucky Coffee Tree

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Sheep, cattle, horses	1 to a few hours	Hours to days; potentially lethal	

Synonyms - American coffee berry, Kentucky mahogany, nicker tree, stump tree

Family - Leguminosae, the bean family.

Habitat

An area bounded by New York, South Dakota, Oklahoma, Tennessee and Virginia. Rich moist woods, bottomland woods, and slopes, creek banks. Most common in western Ohio to Missouri.

Description

- A large tree (60 - 100 feet tall), with rough bark and many major branches. Leaves are bipinnately compound, and the leaflets are stalked, with large ovate shape, feather-like.
- Seven to 13 leaflets per stalk.
- Flowers are greenish-white, small and fragrant, in racemes. Fruits are comprised to pods, brown to maroon, hard, flat and 6 - 10 inches (15 - 25 cm) long and 1 - 1.5 inches (2.5 - 4 cm) wide.
- Seeds (4 - 7) are hard, somewhat flattened, oval, and broad, and 1.5 inches (4 cm) in length.

Toxic Principle

Uncertain, possibly the quinolizidine alkaloid, cytisine, which acts like nicotine.

Toxicity

Sprouts eaten in the spring have produced toxicosis. Pods and seeds on the ground eaten in the fall or winter have produced poisoning. Leaves, young sprouts and seeds with the gelatinous material around them contain the toxin. Sheep, cattle, horses and humans have been poisoned.

Signs

- Generally rapid (< 1 hour) onset of clinical signs.
- Intense gastrointestinal irritation, profuse diarrhea and straining, vomiting, hypertension, bradycardia, respiratory depression, muscle paralysis, and convulsions.
- Animals often display depression.
- Death within a day after clinical signs appear.

Lesions

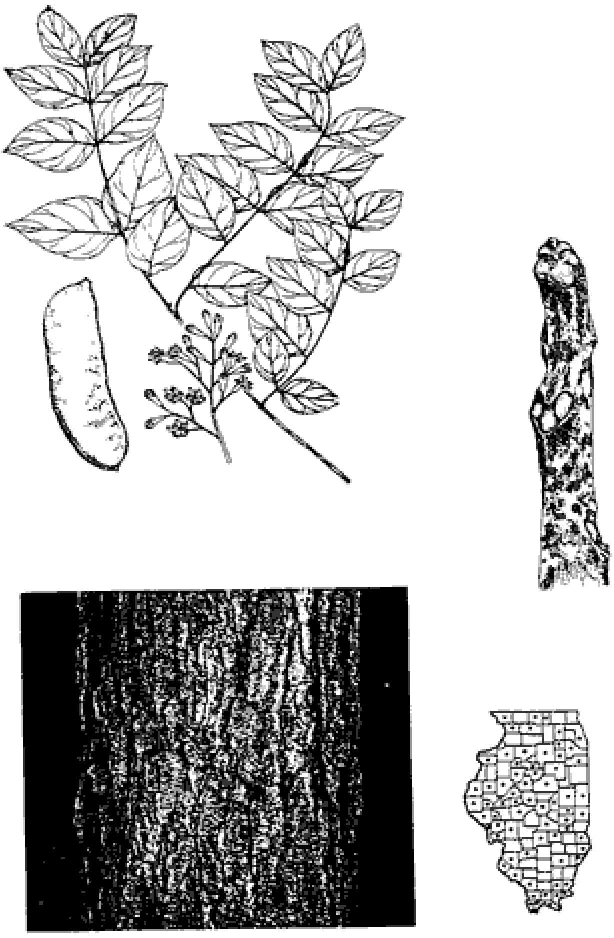
Gastroenteritis, congestion of mucous membranes.

Comments

Humans have been poisoned by using the seeds as a coffee substitute.

Treatment

- Nonspecific, activated charcoal, saline cathartic, supportive and symptomatic.
- Evacuate gastrointestinal tract as condition permits.
- Atropine for parasympathetic signs, e.g., bradycardia.
- Artificial respiration is usually impractical (LA primarily affected), therefore it is important to avoid absorption of highly toxic amounts.
- Treat seizures if develop with diazepam, phenobarbital, pentobarbital, or chloral hydrate in large animal.
- To correct hypotension, fluid therapy may be required.



Kentucky Coffee Tree, *Gymnocladus dioicus* (L.) K. Koch.

Laburnum anagyroides - Golden Chain

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Herbivores	Within a few hours	Hours to 2 days; potentially lethal	

Synonyms - Bean tree, laburnum

Family - Leguminosae

Habitat

Most of the USA and Great Britain. Planted as an ornamental for its hanging racemes.

Description

Large ornamental shrubs or small trees, up to 20 - 30 feet tall, deciduous. Trifoliate, long petioled leaves, alternate with 3 clover-like leaflets, which are downy beneath. Flowers-hanging racemes, 1 1/2 feet long, golden yellow flowers, shaped like sweet peas, 3/4 inch across. Blooms until late spring. Fruit is a legume pod, containing up to 8 seeds, flat, 2 inches long. Root has a licorice taste.

Toxic Principle

The quinolizidine alkaloid, cytisine.

Toxicity

Considered to be the second most toxic tree in Britain. Action is similar to nicotine. Oral toxic dose of seeds in horse is 0.05% of the animal's weight. Cytisine is excreted in the milk. Roots have proven fatal to cattle. Young pods and seeds are highly toxic. Humans also poisoned.

Signs

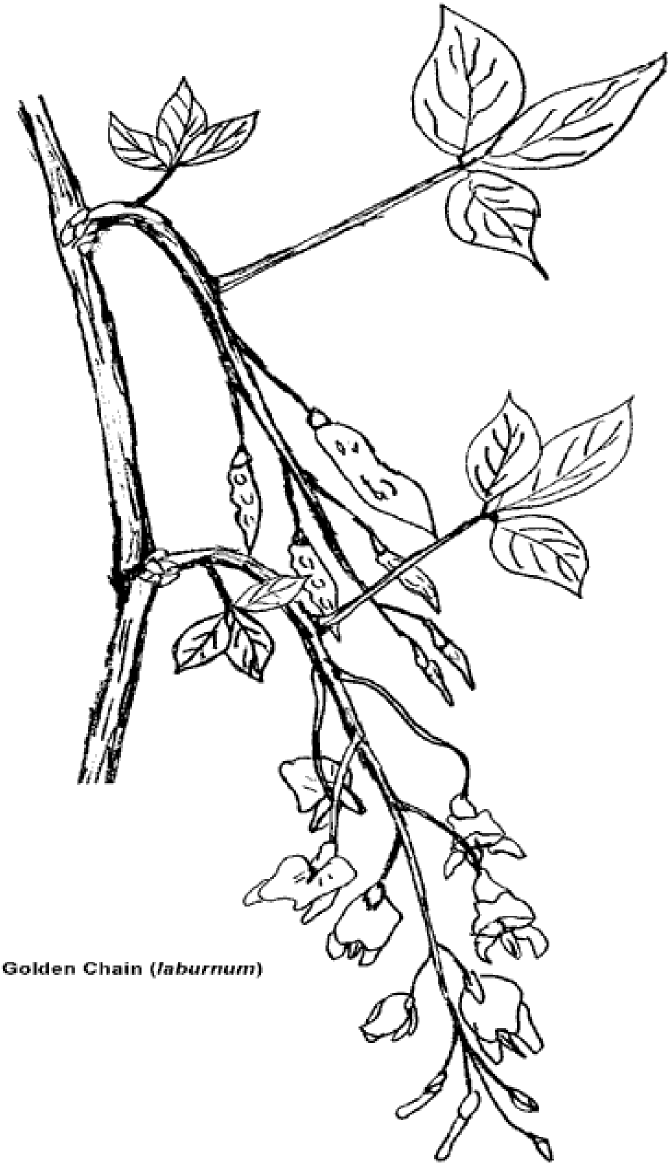
- Excitement, incoordination, convulsions, coma and death due to asphyxiation.
- Additional signs include nausea, vomiting, diarrhea, and mydriasis.

Treatment

Same as for nicotine toxicosis.

Prevention

The likelihood of toxicosis can be reduced by removal of the flowering portion shortly after blooming.



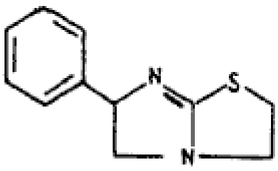
Golden Chain (*laburnum*)

Levamisole

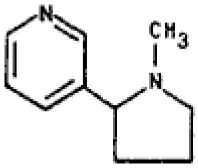
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Horses, cattle, sheep, swine, dogs, marine mammals	Minutes to a few hours	Unlikely to be lethal	

Introduction

Levamisole is 1-2,3,5,6-tetrahydro-6-phenyl-imidazo [2,1-b]-thiazole hydrochloride. It is a white crystalline powder that is highly water soluble.



Levamisole



Nicotine

Uses

Anthelmintic, microfilaricide, immunostimulant.

Mechanism of Action

Depolarization of nerve cell membranes. Proposed to act as a nicrotine-like ganglionic stimulant. It may have both nicotinic and muscarinic effects at cholinergic receptors. First there is stimulation, then blockade of the ganglionic and skeletal muscle transmission.

Toxicity

- Sheep (oral):
  - 5 times therapeutic dose-signs begin.
  - Therapeutic dose = 8 mg/kg.
  - Oral lethal dose = 90 mg/kg.
- Swine:
  - > 5 times therapeutic dose in feed or > 3 times therapeutic dose in water-signs begin.
  - > 4 - 8 times therapeutic dose with SQ route-signs begin.
  - Therapeutic dose = 8 mg/kg.
  - SQ lethal dose = 40 mg/kg.
- Cattle:
  - > 3 times therapeutic dose-signs begin.
  - > 2 times therapeutic dose with SQ route-signs begin.
  - Therapeutic dose = 8 mg/kg.
- Dogs:
  - ≥ 4 times therapeutic dose-signs begin.
  - Therapeutic dose = 10 - 11 mg/kg.
- Horses:
  - ≥ 2 times therapeutic dose - signs begin.
  - Therapeutic dose = 7.5 - 15 mg/kg.
- The metabolites are less toxic than the parent compound.

Contraindications

- Nicotine and nicotine-like agents may enhance the toxicity of levamisole thus decreasing the LD_{50}.
- Not approved for use in lactating dairy cattle.
- No adverse effects have been reported with concurrent use of topical diazinon or malathion.

Clinical Signs

- Cattle, sheep, goats, swine, and horses:
    - Hypersalivation (may have muzzle foaming in cattle at normal dose for a few hours), head shaking, lip licking, vomiting in swine, muscle tremors, ataxia, anxiety, hyperesthesia, irritability, clonic convulsions, CNS depression, rapid respiration, dyspnea, frequent urination, frequent defecation, collapse, prostration.
    - Death usually due to respiratory failure.
- In sheep and goats, the onset of signs occurs within 15 minutes, effects peak by about 30 minutes, and recovery occurs within 1 - 6 hours.
- In swine, a subcutaneous overdose may lead to dyspnea and death within 5 - 60 minutes.
- Dogs:
    - Vomiting, hypersalivation, depression, diarrhea, anorexia, cardiac arrhythmias, dyspnea, behavioral changes, pulmonary edema, tachypnea, ataxia, muscle tremors, seizures, death due to respiratory failure.
    - Hemolytic anemia has occurred in some dogs due to repeated dosing.
    - Also, this may cause an increase in alkaline phosphatase due to a change in osteogenesis.

Lesions

Congestion of the splenic red pulp, neutrophilic infiltrates in the lung parenchyma, marked subepicardial hemorrhage, intense enteritis, acute hepatic degeneration with marked subcapsular hemorrhage, massive hepatic necrosis, thalamic hemorrhage.

Residues

- The fat, muscle, and blood are free of detectible residues within 24 hours after ingestion of feed or water.
- The liver is free of residues within 72 hours.
- Label recommendations should be followed for proper use and withdrawal times.

Diagnosis

This is made primarily by a history of an overdose being administered, onset, and manifestations of clinical signs.

Treatment

Decontamination-emesis is recommended if possible within 1 hour of ingestion. After vomiting has subsided, activated charcoal and a saline cathartic are recommended. Careful monitoring of the patient is critical. Symptomatic and supportive therapy is of value if signs of significant intensity develop. This may include fluids, oxygen, and artificial respiration as indicated. Atropine has been suggested as an antagonist, but it does not decrease mortality. If needed, control seizures with diazepam or a barbiturate.

Imidacloprid

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Small animals?	Minutes to hours	Unlikely to be lethal	

Advantage ®, Premise ®, and Merit ®. More potent agonist at nicotinic receptors of arthropods than those of mammals.

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5. Nicotinic antagonists

Succinylcholine and nicotinic antagonists

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)
Succinylcholine	All species	Minutes	Minutes; potentially lethal	

Succinylcholine is a nicotinic antagonist used during surgery to block neuromuscular junction receptors and produce paralysis and thus muscle inactivity. It is structurally similar to acetylcholine.

Toxicants that Cause Paresis or Paralysis

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Black Widow Spider (*Latrodectus* spp.)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
All species	Within 6 hours	Hours; infrequently lethal	

Black widow spider (*Latrodectus mactans*) and other *Latrodectus* spp., e.g. brown widow spider, red widow spider, and red-legged spider.

Description

- Medium-sized (10 - 18 mm) spider, black widow abdomen is shiny black with a red hourglass or red spots.
- Both male and female are poisonous, however, only females' mouth parts are of sufficient size to penetrate skin (human).

Distribution

- Widely distributed in the warmer portions of the USA. Red widows reportedly occur in Florida.

Toxic Principle

- Several biologically active proteins identified including neurotoxins.

Mechanism of Action

- One lethal fraction, alpha-latrotoxin, causes release and depletion of acetylcholine.
- Binds to glycoproteins or gangliosides on neuromuscular synaptic membranes, allowing cationic ion-channels to remain open. Results in depolarization and calcium-independent release of neurotransmitter. Inhibits presynaptic neurotransmitter reuptake.
- *In vitro*, the sharp increases in nerve potentials are followed by a decline until no nerve impulses occur.

Clinical Signs

- Dull numbing pain at sight of injection of venom, muscle cramps, muscle fasciculations, tonic clonic convulsions, sweating, excess salivation, flaccid paralysis.
- Weakness with dyspnea followed by paralysis may occur within 6 hours in an acute case.

Treatment

- Corticosteroids, IV fluids, prophylactic anitibiotics.
- Methocarbamol, calcium gluconate, meperidine, and atropine may be used to control muscle spasms, pain, and excessive secretions.
- Most envenomations are self-limiting and clinical signs resolve within 4 - 6 hours.
- Black widow spider antivenom (Wyeth Laboratories) is available.

Neuromuscular Blocking Agents

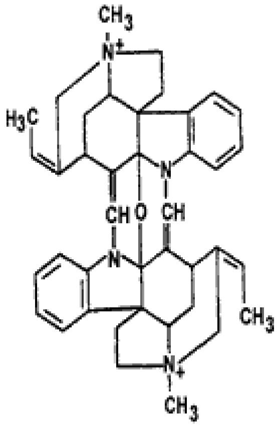
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
All species	Minutes	2 - 4 hours; potentially lethal	

Introduction

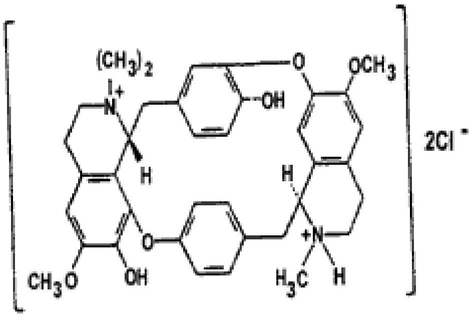
- Neuromuscular blocking agents are drugs that decrease the response to acetylcholine at the neuromuscular junction of skeletal muscle tissue.
- These drugs are classified into depolarizing (e.g., succinylcholine chloride) or nondepolarizing (e.g., curare) agents on the basis of their mechanism of action.

Source

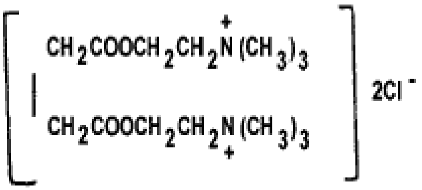
- Nondepolarizing agents:
  - Curare is a generic term for various South American "arrow poisons". Derived from various *Strychnos* and *Chondrodendron* plant species.
  - The active alkaloids in curare are quaternary amines which induce a neuromuscular blocking effect.
  - Nondepolarizing ("curare-like") skeletal muscle blocking agents include tubocurarine, vecuronium, pancuronium, atracurium, and others. Predominately used for skeletal muscle relaxation after general anesthesia has been induced.
- Depolarizing agents:
  - Decamethonium.
  - Succinylcholine chloride-primarily used as a skeletal muscle relaxant.



Curarine-I



(+)Tubocurarine Chloride



$$\left[\begin{array}{l} CH_2COOCH_2CH_2\overset{+}{N}(CH_3)_3 \\ | \\ CH_2COOCH_2CH_2\underset{+}{N}(CH_3)_3 \end{array}\right] 2Cl^-$$

Succinylcholine

Mechanism of Action

- Nondepolarizing agents:
  - Combine with the cholinergic receptor at the postjunctional membrane of skeletal muscle and thereby competitively blocks the transmitter action of acetylcholine.
  - Compete with Ach for cholinergic receptors at autonomic ganglia.
  - Decrease Ach release by presynaptic cholinergic nerve membrane.
  - May also cause the release of histamine with resultant effects.
- Depolarizing agents:
  - Stimulate sympathetic ganglia.
  - Have high affinity for postjunctional Ach receptor sites; stimulation followed by a depolarized blocked postsynaptic receptor. Resistant to acetylcholinesterase as compared to acetylcholine.
  - Less effective at stimulating release of histamine.

Signs

- Motor weakness followed by total flaccidity and inexcitability of the muscles.
- Small rapidly moving muscles or the jaws, ears, eyes are affected first and later the limb and trunk muscles become involved.
- Finally, intercostal muscles and the diaphragm are paralyzed resulting in terminal asphyxia.
- Terminal convulsions, if they occur are probably hypoxic in origin and very weak due to muscle effects. Generally have no direct CNS effects.
- Bronchospasms, hypotension, and excessive bronchial or salivary secretion may be a result of histamine release. Hypotension may occur due to direct actions.
- Malignant hyperthermia has been reported in man, swine, and horses and is more likely when muscle relaxants are used during surgery.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Quarternary ammonium neuromuscular blocking agents are poorly absorbed from GI tract.
- Nondepolarizing agents undergo variable metabolic degradation by liver.
- Succinylcholine is hydrolyzed by butyrylcholinesterase of liver and plasma to less pharmacologically active agent succinylmonocholine.

Treatment

- Usually the effects last up to 4 hours and generally less. Therefore the use of artificial respiration as needed may be sufficient to allow survival in some animals.
- Reversal of nondepolarizing agents neuromuscular blockade by administration of cholinesterase inhibitor, e.g., neostigmine.

Note - Because cholinesterases normally degrade succinylcholine, neostigmine and other cholinesterase inhibitors should not be concurrently administered with this depolarizing agent.

Note - Considerable study and experience are recommended prior to the use of curariform drugs. Taylor, in Goodman and Gilman, editors, The Pharmacologic Basis of Therapeutics, recommends their use only by individuals with "extensive training in their use and in a setting where facilities for respiratory and cardiovascular resuscitation are immediately at hand". This text is recommended for those contemplating the use of these agents.

Delphinium - Larkspur

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Mostly cattle	1 - 4 hours	Often rapidly lethal	

Introduction

- Most Larkspur poisoning occurs in the western USA.
- Synonyms include poison weed and stagger weed.

Habitat

- Majority of Larkspur species are found west of the Mississippi River.
- Western USA, 2 major groups based upon growth characteristics.
  - Dwarf-low larkspurs occur in lowland slopes and grasslands. Less than 3 feet in height.
    - Include *D. nelsonii*, *D. geyeri, D. virescens*, and *D. bicolor*.

        - Tall larkspurs-upper slopes and among open stands of trees in draws. Are 4 - 6 feet in height. Generally occur in high altitude.
            - Include *D. barbeyi, D. occidentale, D. glaucum*, and *D. trolliifolium*.
- Eastern USA.
    - *Delphinium tricorne*.
        - Occurs in moist wooded areas-e.g. ravines and along streams.
        - Occasional poisoning-East Central USA.
- Also in cultivation as garden perennials.

Description

- Most are perennial, herbaceous, erect herbs. Simple or branching stems.
- Palmately lobed or palmately divided alternate leaves.
- Flowers are blue, purple or white, in a terminal raceme above the leaves; with a prominent spur formed from 1 sepal + 2 petals.
- Clustered (3 - 5 follicles) fruits contain irregular, ridged, brown seeds.

Toxic Principle

- The polycyclic diterpene alkaloid methyllycaconitine is the principle toxic alkaloid.
- In *D. occidentale* and *D. barbeyi*, the alkaloid content is high in early growth and then drops rapidly so poisoning is rare after flowering, unless the toxic seeds are ingested. Poisoning generally in spring and fall.
- Nevertheless-dried plants are poisonous-so drying alone is apparently not the cause of detoxification.

Mechanism

Methyllycaconitine functions as a potent neuromuscular blocking (curare-like) agent. Acts at postsynaptic, nicotinic, cholinergic receptor in the CNS and at neuromuscular junctions.

Toxicity

- LD_{50} cattle 0.5% bw. *D. barbeyi* can cause fatalities in cattle at 17 g green plant/kg bw.
- May occur on any range but is more common when ranges are overgrazed.

Susceptible Species

- Causes more cattle losses than any other plant on western ranges.
- Horses and sheep rarely affected. Sheep are less susceptible than cattle.
- Grazing an area with sheep will not make it safe to subsequently graze cattle. Sheep eat different parts of the larkspur plant than cattle.

Signs

- Most common clinical sign in cattle may be sudden death.
- Clinical signs are primarily related to the nervous system.
- Hyperirritability, confusion, nausea.
- Mild muscle tremors, stiffness, weakness.
- May see constipation, bloat, oral irritation, vomiting (or regurgitation), salivation which may be followed by a dry mouth.
- Collapse, prostration. Inhalation pneumonia common in recumbent animals as a result of vomiting.
- Convulsions.
- Death is a result of respiratory paralysis or bloat as animals often fall into recumbency with the head downhill. Fatalities usually occur within 3 - 4 hours of ingestion of a fatal dose.

Note - Cardiovascular disturbances including hypotension and myocardial depression and associated arrhythmias may be difficult to manage pharmacologically. The arrhythmias may be comprised of supraventricular tachycardia and conduction disturbances.

Postmortem

Nonspecific lesions including ruminal bloat, venous congestion, inhalation pneumonia, and GI inflammation.

Prognosis

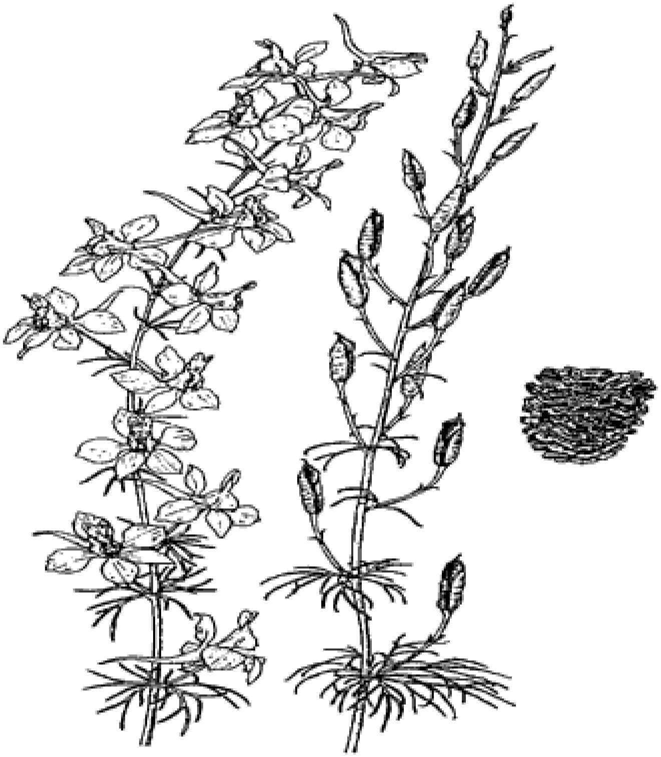
Guarded even in mildly affected.

Treatment

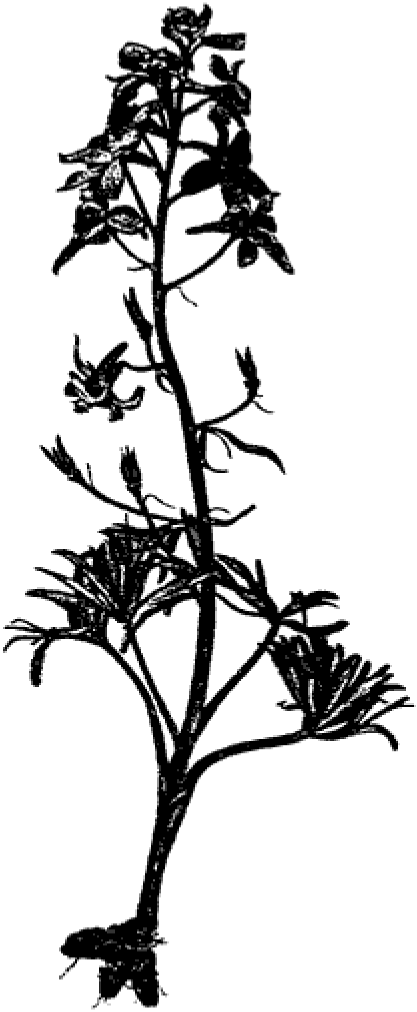
- Activated charcoal, magnesium sulfate as a saline cathartic.
- Excitable range cattle may be left untreated and moved to a new pasture.
- Physostigmine (0.04 to 0.08 mg/kg bw IV) is effective as a treatment for larkspur poisoning. Best if given early, and repeated injections are generally necessary.
- Turn so head is uphill.
- Relieve bloat, antibiotic therapy for inhalation pneumonia.

Prevention

- Spot spraying of larkspur patches with herbicides, followed by attempts to revegetate with other types of plants (i.e., grass).
- Some sources report $10,000 per year (in an average cow herd) in 500 losses and management costs due to poisoning.

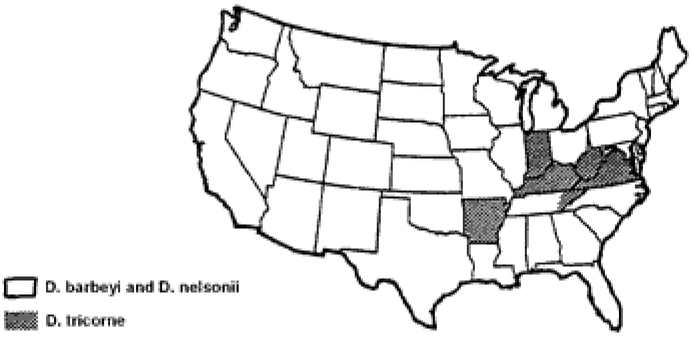


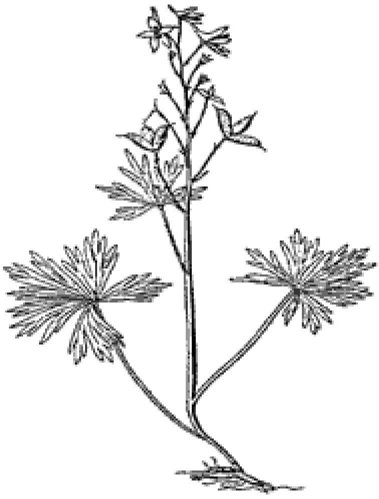
Cultivated Larkspur - These plants have finely divided leaves, blue to white or pink spurred flowers, a dry splitting seed pod, and a rough seed (enlarged, right center).



Low Larkspur (*Delphinium Menziesii).* This is the most common of the low larkspurs, extending from Colorado to the Sierras, and causes heavy losses of cattle.

Distribution of Larkspur





Dwarf larkspur (*Delphinium tricorne*), one-third natural size.

Tall larkspur (*Delphinium trolliifolium*) - This is the tall larkspur of the Northwest, and is conspicuous because of its large and beautiful flowers.

Botulism

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Most species; especially waterfowl	12 - 48 hours	Days to months; often lethal	

Introduction

- Botulism is the disease caused by any one of 7 serotypically different, but functionally similar toxins produced by strains of *Clostridium botulinum*. They are among the most potent toxins known. Of these 7 serotypes (A-G), types C and D have historically been the most commonly implicated in domestic mammals and poultry. These proteinaceous toxins are only slightly cross-reactive and can generally be regarded as immunologically specific.
- Serotypes of *C. botulinum* toxins:
    - A, B serotypes: primarily isolated from soil. B serotype has been a problem especially in horses, and also is implicated in toxicoses of cattle. Most often implicated with human infant botulism.

    - C serotype: is the most commonly implicated serotype in dogs, waterfowl, and poultry. Reports now also implicate this toxin in horses.
    - D serotype: birds are somewhat resistant to type D, but cattle are quite sensitive.
    - E serotype: isolated from mud and water of estuaries and sea food. Dogs are reportedly extremely sensitive to type E toxin.

Sources

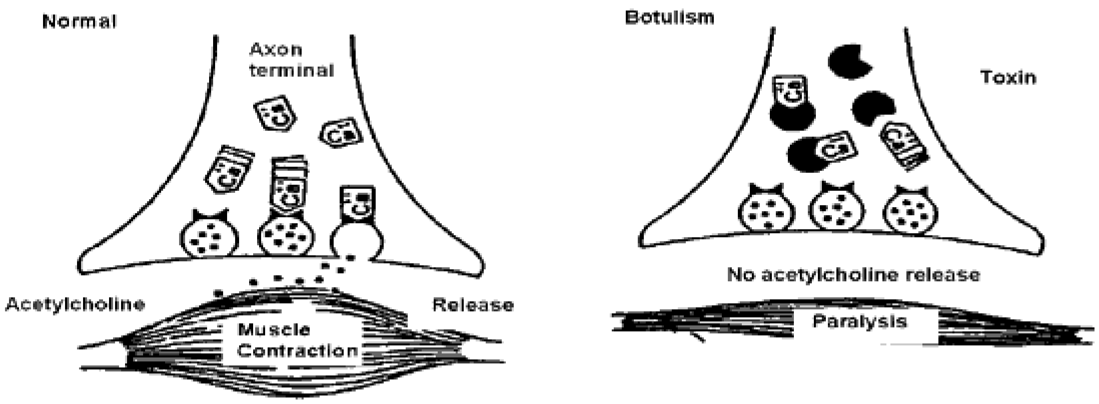
- The most common source of botulinus toxin causing poisoning in most if not all species of domestic animals is carrion. Carcasses of decaying animals form an anaerobic environment and the toxin may be present in maggots feeding on the contaminated tissus.
    - Waterfowl: Decaying vegetation and invertebrates in flooded areas or other stagnant water, such as ponds, may serve as the primary source of botulinus toxin causing death in the first affected birds. Subsequently, birds which are simultaneously poisoned and inoculated with *C. botulinum*, become the anaerobic carcasses for additional toxin production and the source for additional animals to become poisoned. This often results in a mass die off due to botulism. Maggots often serve as the vector of botulinus toxin.
        - Treatment: Drain areas, remove dead birds, frighten off incoming birds temporarily.
    - Carnivores: Carrion.
    - Cattle: Carrion incorporated into feed is one source (dead rodents or other animals in feed bins). "Osteophagia", the eating of the bones of dead animals associated with hypophosphatemia, is another source that occasionally results in botulism (sometimes referred to as "loin disease"). Adding pond water, from a stagnant pond, to corn silage resulted in a massive, highly lethal episode of botulism in dairy cattle.
    - Feeding poultry litter is a strongly suspected cause of botulism in ruminants in Australia.
    - Horses: Horses are extremely sensitive to the effects of botulinus toxin and suffer from toxicosis as a result of incorporation of carrion into their feed, as well as "toxicoinfectious botulism". The latter is a result of colonization of necrotic tissue in the animal by *C. botulinum* organisms and apparent production of toxin *in situ*. Sites may include the navel, wounds, gastric ulcers and possibly other necrotic areas, such as foci of necrosis in the liver and the gut in association with such problems as sand ingestions. Botulism has not been reproduced by the feeding of *C. botulinum* to healthy horses. "Toxico infectious botulism" (Shaker foal syndrome) of horses has been associated primarily with *C. botulinum* type B toxin. Signs suggestive of botulism have been reported in horses fed haylage. Proof of botulinus toxin involvement remains to be demonstrated in these cases.
    - Affected foals are typically less than 8 months of age and are commonly less than 2 months of age.
    - Humans: Three forms of the disease occur as a result of: 1) Ingestion of preformed botulinus toxin in improperly canned foods, especially in high protein foods such as meats and beans; 2) Wound botulism; and 3) Infantile (gastrointestinal) botulism. An association has been made with the latter and the feeding of honey.
- General:
    - Affected animals may shed *C. botulinum* spores in their feces which may result in further environmental contamination.

Toxicity

- One of most toxic compounds known, particularly on a mole/kg basis. Because of its high molecular weight, botulinus toxin is 36 times as toxic as parathion on a mg/body weight basis, but over 100,000 as toxic on a molecule/body weight dosage basis.
- LD_{50} mouse 0.3 mg/kg bw; minimal LD mouse 0.12 mg/kg.
- A single maggot from a dead pheasant was sufficient to kill a 3 week old chicken.

Mechanism of Action

- Botulinus toxin enters presynaptic membranes of cholinergic nerve endings via receptor mediated endocytosis. The toxin acts intracellularly via a metalloendoprotease action to cleave 3 proteins essential for neurotransmitter release (synaptobrevin, syntaxin, and SNAP-25). Thus, the toxin inhibits degranulation or exocytosis of acetylcholine granules. A small number of molecules of this toxin binds irreversibly to the sites of action, producing an essentially irreversible cessation of all cholinergic transmission. Death results from respiratory failure.



Schematic drawing of the blockage of acetylcholine release by botulinal toxin at the neuromuscular junction. The toxin prevents exocytosis of acetylcholine. From: Greene CE. Clinical Microbiology and Infectious Diseases of the Dog and Cat. WB Saunders, 1984.

- Lower motor neuron effects include paresis to paralysis, hypotonia and hyporeflexia.
- Some pharmacologic actions of various botulinus toxins and specific binding difference between toxins indicate the possibility of different mechanisms of action.

Signs

- Myasthenia.
- Inability to swallow.
- Progressive muscle paralysis with muscle weakness first in the hindquarters and then progressing to the forequarters, then the head and neck become involved. Humans are atypical in that in some aspects the effects are descending in sequence.
- Humans:
  - Latent period after ingestion of preformed toxin is from 2 hours to 8 days; usually 12 - 48 hours.
  - In 1949 over 60% of human victims died, but by 1980 only 13 - 15% succumbed.
  - Early vomiting indicates a greater degree of exposure and may be a cause of aspiration pneumonia.
  - Bilateral cranial nerve involvement and double vision. Pupils dilated and fixed or normal size and fixed.
  - Diarrhea, then obvious constipation.
  - Nasal voice. Dry painful mouth.
  - Weak neck muscles and limbs
  - Drowsy, but otherwise mental processes seem normal.
  - Death due to respiratory paralysis.
- Birds: All Anseriformes (waterfowl) are susceptible (other species vary).
  - Signs start with the progressive paralysis of the neck (**limberneck**), legs and wings.
  - Gasping for air and sometimes greenish diarrhea.
  - Usually die in coma within 24 - 48 hours due to respiratory and circulatory failure.
  - May drown from inability to hold head and body in normal positon.
- Birds (Pheasants):
  - Pheasants exhibited paralysis of the legs, labored breathing and diarrhea.
  - Type C antisera was able to prevent the disease.
- Dogs:
  - General weakness is followed by an ascending paresis and paralysis with cranial nerve involvement (facial paralysis may be present). Remain alert and responsive, wag tail and move head even when paralyzed. (In this respect is the same as tick paralysis and "coonhound paralysis" [polyradiculoneuritis]; however in the latter conditions, there is less cranial nerve involvement than with botulism)
  - Mydriasis with slow pupillary reflexes, decreased palpebral reflexes.
  - Poor jaw tone, dysphagia. Vomiting, pain in cranial abdomen.
  - May have secondary dehydration and/or urinary tract infections as well as secondary respiratory infections.
  - Occasionally may have slow heart rate, rarely see megaesophagus and associated regurgitation. Decreased gag reflex.

- Cattle:
    - Inability or decreased ability to stand. Sternal and sometimes subsequent lateral recumbency. Often down with head down or turned to the side, like a cow with milk fever, may die in sternal recumbency.
    - Rumen motility decreased or absent.
    - Hypersalivation. Paralysis of muscles of mastication and cannot resist forced opening of the mouth.
    - Tongue may have normal tone, but often exhibits varying degrees of flaccid paralysis. This is most apparent after pulling the tongue out of the mouth repeatedly.
    - Urinary bladder distended: with severe toxicosis become less likely to urinate when "feathered" or may not urinate at all until stimulated by attempts to introduce a urinary catheter.
    - Proteinuria in some cows exhibiting paresis or paralysis.
    - Concentrated urine and reduced rumen fill indicate decreased ability to drink water and resultant dehydration. Dry feces with large amount of mucus.
    - Slow pupillary response to light.
    - Animals sense pain stimuli but withdrawal reflexes from pin pricks or other pain are weak or absent.
    - Rectal temperature, heart rate and respiratory rate remain normal until late in the syndrome.
    - Death occurs without agonal respiratory gasps.
    - Deaths in a herd may occur in one to several cows per day every day or every few days.
    - Hyperglycemia may be noted.
- Foals and Horses:
    - Progressive symmetrical muscle paralysis, with stilted gait.
    - Muscle tremors, inability to remain standing for longer than 4 - 5 minutes, drop to sternum. If helped to feet after a rest, signs reoccur and duration of standing decreases as time progresses.
    - Dysphagia: In foals, milk runs out of their mouths as they attempt to suckle. Difficulty swallowing water, tongue and pharyngeal paralysis. Loss of tongue tone is often an early clinical sign in adult horses.
    - Reduced intestinal peristalsis. Constipation. Frequent attempts to urinate with voiding of only a few ml of urine.
    - Mydriasis.
    - Later see dyspnea with extension of the head and neck. Tachycardia.
    - Respiratory arrest, generally after a period of lateral recumbency, with the neck extended.
    - Generally, the body temperature and hemograms remain normal throughout the syndrome.
    - Creatine kinase may be elevated due to prolonged recumbency.
    - Mortality is high in all ages, and is greater than 90% in foals. Foals less than 3 weeks old usually die within 24 hours and those 4 weeks or older live up to 72 hours.

Lesions

- In all species, lesions are generally nonspecific.
- Cattle:
    - Abomasal hyperemia.
    - Fluid-filled large intestine.
    - Aspiration pneumonia may be present.
- Horses:
    - Abscesses may occur in the navel, the lungs or in wounds of the skin or muscle. These may be sites of toxin production.
    - Foci of necrosis may occur in the liver.
    - Gastric ulcers may be present at the margo plicatus or less often at the pyloris.
    - Congestion and edema of the lungs.
    - Excessive pericardial fluid with free floating strands of fibrin.
    - Often there is generalized fatty change of the liver.
    - The urinary bladder is often distended with urine.
    - Aspiration pneumonia is sometimes present.
    - The rectum is often filled with hard, mucus-coated feces.
    - Occasionally the mare and foal are both affected and in such cases, the mare often has adrenocortical hyperplasia.

Diagnosis

- Most species:
    - Diagnosis is difficult to confirm. The mouse inoculation test is becoming obsolete but some labs may still use it. Tests for botulinus toxin can be used in cases where the animal is still alive or has just died. After a longer postmortem interval, the carcass may no longer represent the antemortem state.
    - Mouse inoculation test:
    - Positive test is manifested by a "wasp-wasted" appearance with respiratory distress and progressive paralysis and death within 24 hours in most cases.
    - Specimens to test include: food, carrion, maggots, spoiled bone meal, silage, bones, decaying vegetation; serum, gastrointestinal tract contents, feces, etc.
    - These specimens may be tested to determine if the toxin is present by the mouse inoculation test and may also serve as materials for the culture and identification of *C. botulinum*.
    - Mouse inoculation/protection test procedure: Mice are inoculated with a suspect specimen with and without a specific or polyvalent antiserum. The production of typical botulism, and concurrent protection of the appropriate antitoxin treated mice allow delineation of the specific toxin type.
- An immunodiffusion test using agar impregnated with antitoxins may sometimes be recommended as an alternative to the mouse protection test. One of the best labs is at the College of Veterinary Medicine of the University of Pennsylvania.
- Poultry labs are generally set up to run tests to identify the Type C toxin, commonly implicated in small animals.
- Type D toxin is difficult to isolate, and therefore it may be more practical to reproduce the syndrome in 1 group of animals with comparison to toxoid-vaccinated groups rather than through the usual practice of antitoxin administration.
- Culture:
    - Under the microscope, the bacteria appear as single or short chains of rod-shaped organisms. They are slightly motile via the action of 4 - 20 flagella.
    - One isolation medium that has been recommended is 25 x 200 mm tubes of chopped meat glucose starch (CMGS) medium made with freshly ground horse meat. A 2 - 3 gram sample of necrotic tissue or other specimen is cultured in duplicate tubes of such medium. The tubes are heated for 15 minutes at 70 ºC in an attempt to kill bacterial contaminants. One tube is incubated at 30 ºC and the other at 35 ºC for 5 days. Routine culture methods may also be used for initial isolation from most specimens but check on laboratory capabilities.
- Horses:
    - Serum from horses generally will not have enough toxin present to be of value in the mouse inoculation test. This is the case because the horse is more sensitive to the toxin than are mice and the concentration of toxin in lethally affected horses will not affect the test mice. Because of the difficulties of the test procedures, tentative diagnoses may be the only possible diagnoses in some cases.

Differential Diagnosis

- Cattle:
    - Mineral imbalances (Ca or Mg deficiencies), including parturient paresis.
    - Other paralytic toxicoses (cholinesterase inhibitors and many others).
- Horse:
    - Dysphagia-esophageal or pharyngeal obstruction, leukoencephalomalacia, yellow star thistle, rabies.
    - Tick paralysis, hypocalcemia, white snakeroot poisoning.

Treatment

- In cases of recent ingestion of preformed botulinus toxin, measures to remove the contents of the gastrointestinal tract as well as activated charcoal and a cathartic are indicated.
- Antitoxins are the product (serum) of an animal (horse), which has received injections of a toxoid (inactivated toxin). Use of polyvalent antitoxin early in the course of the syndrome greatly enhances survival rates. The following dosage schedules have been recommended.
    - Horse:
        - 200 ml for foal and 500 ml for adult (> 400 lb bw).

    - Debride and treat any deep wounds.
    - Sodium/potassium penicillin 22,000 - 44,000 IU/kg QID IV to eliminate proliferating *C. botulinum* organisms. Oral penicillin therapy as well as aminoglycosides and tetracyclines are contraindicated in the horse.
  - Dog:
    - Trivalent antitoxin used in human medicine contains type A, B, and E antitoxins, if available type C antitoxin should be used but may be difficult to obtain.
    - 5 ml of a polyvalent antitoxin was administered IV and IM to a coonhound with type C botulism.
    - Antibiotic therapy with 20,000 IU/kg penicillin IM BID and ampicillin 16 mg/kg PO or 8 mg/kg IM QID has been recommended.
- Supportive care including padding, provision of a warm, dry environment and turning the animal with assistance in eating, drinking, urination and defecation are indicated. Supportive alimentation is required in a large number of cases. Prolonged ventilation for respiratory paralysis is probably not going to be practical for any animal patient.
- The possibility of respiratory or urinary tract infections should be reason for frequent monitoring and, if necessary, appropriate therapeutic measures.
- In cattle, carbamylcholine to stimulate gastrointestinal motility and enhance removal of the toxin seemed to enhance the probability of survival in a small number of animals.
- The use of guanidine HCl at 15 - 30 mg/kg/day orally in divided doses to increase the release of acetylcholine has been debated. Is not advocated for therapy.
- 4-aminopyridine at 2 - 3 mg/kg IP reversed the paralysis due to botulism in rats.
- Recently a therapeutic regimen of cholinesterase inhibitors, such as physostigmine and neostigmine, have been recommended along with atropine sulfate to block the muscarinic effects of the cholinesterase inhibition. Such measures should be used only in life-threatening toxicoses and with the utmost caution!

Recovery

Recovery in dogs may occur within 14 days or longer. Recovery of function occurs in the reverse order of the loss of function during the development of the syndrome.

Notes

- Mares on a high-protein, reasonably high caloric diet are believed to be predisposed toward having foals with toxicoinfectious botulism. Therefore, a less concentrated diet may be indicated on such farms.
- Secretion of corticosteroids by the mare has been postulated as contributing to the development of toxicoinfectious botulism in the suckling foal.

Tick Paralysis

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Cattle, sheep, dogs, cats, deer, llamas	3 - 9 days	Days sometimes lethal	

Introduction

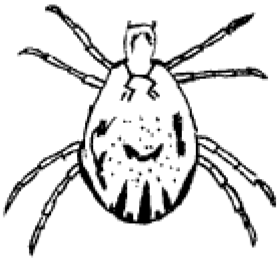
- Ticks and mites are important arachnid ectoparasites of humans and animals and have a well-established role in the transmission of certain diseases.
- A number of tick species have been reported to cause paralysis.

Source

- Female ticks of certain species, especially *Dermacentor andersoni* or *D. variabilis*, in the USA secrete a neurotoxin from their salivary glands when feeding. *Ixodes holocyclus* and other *Ixodes* spp. as well as

Amblyomma spp. have been implicated in tick paralysis in Australia. Autonomic involvement (cardiovascular) with *Ixodes* has been reported.

- Similar condition reported due to soft ticks of poultry and is primarily due to immature tick forms.



Dermacentor

Toxicity

- One feeding tick is enough to cause clinical signs.
- Cases of tick paralysis coincide with seasonal activity of ticks in a given geographical region.

Mechanism of Action

- Affects the lower motor neuron.
- Either inhibits depolarization of the terminal portion of motor nerves or blocks the release of acetylcholine at the neuromuscular junction. Electrophysiologic parameters favor the former site of action. EMGs show depressed evoked muscle potentials and slowed transmission across the neuromuscular junction. Nerve conduction velocity is consistently lowered.
- Result is paresis to paralysis and hypotonia as well as hyporeflexia.
- May have CNS effects as well.

Susceptible Species

Cattle and sheep have been commonly affected in the northwestern United States. Horses have been less commonly affected, but paralysis can result from 1 female tick. Reported more commonly in dog, rarely in cat. Wildlife rarely affected, however mule deer have been affected experimentally.

Signs

- Onset is generally 3 - 9 days after the attachment of the tick. Clinical signs may be transient or intermittent if the feeding ticks disengage and fall off. Female ticks found on the body, look carefully.
- Paresis begins in the pelvic limbs and ascends.
- Ataxia may be an early clinical sign. Animals may appear apprehensive and will assume a wide-based stance.
- Signs become generalized within 1 or 2 days.
- Cranial nerve dysfunction is not usually prominent and, if present, is usually limited to facial nerve diplegia (bilateral paresis or paralysis) and mild depression of gag reflexes. In some cases, mydriasis and anisocoria may occur as may dysfunction with other cranial or peripheral motor nerves.
- Dogs may develop anorexia and a change in phonation may be noted.
- Animals generally remain bright and alert unless secondary complications such as dehydration or infection occur.
- Respiratory paralysis can occur within 5 days of the onset of signs.
- There are usually no sensory deficits.

Diagnosis

- Finding feeding female ticks of the *Dermacentor* or other toxigenic genus.
- Nerve conduction velocity is consistently slower than normal.
- EMG changes appear approximately 5 days after onset of peripheral weakness.

- No notable effects on hematology, blood chemistry, or cerebrospinal fluid parameters occur in uncomplicated cases.
- Recovery upon removal of the ticks and the lack of reoccurrence in their absence confirms the diagnosis.

Lesions

None.

Treatment

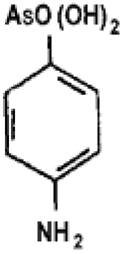
- Removal of the tick or ticks results in marked improvement within 24 hours followed by complete recovery within days.
- It is essential to examine the ear canals closely, as well as the ear folds and interdigital areas in order to remove all ticks.
- Even when no ticks are found, but the signs are still suggestive of tick paralysis, a tick dip solution may be indicated.
- Assisting respiration could be necessary in severe cases, it may be essential to continue this assistance for up to several hours.
- Immunity to *D. andersonni* toxin has not been demonstrated.

Phenylarsonics

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Swine, poultry	Days	Weeks to permanent damage (common); potentially lethal	

Source

- Four Compounds:
  - Arsanilic acid (p-aminophenylarsonic acid) and its salt, sodium arsanilate.
  - 3-nitro-4-hydroxyphenylarsonic acid (Roxarsone; or "3-Nitro").
  - 4-nitro-phenylarsonic acid (Nitarsone or Histostat-50).
  - p-ureidobenzenearsonic acid (Carbarsone or Carb-o-sep).
- Phenylarsonics are used as feed additives for disease control and to improve weight gain and feed efficiency. Had been used previously for blood parasites.
- Recommended concentrations:
  - Arsanilic acid (AA) and sodium arsanilate:
    - 50 - 100 ppm (0.005 - 0.01%) 45 - 90 gm/ton prolonged feeding for weight gain and feed efficiency in swine and poultry (chickens and turkeys only).
    - Late gestating sows require approximately 45 ppm because of their increased feed comsumption.
    - 250 - 400 ppm (0.025 - 0.04%) for 5 - 6 days for treatment of swine dysentery.
  - 3-Nitro:
    - 25 - 37.5 ppm for swine diets to improve weight gain and feed efficiency.
    - 200 ppm for 5 - 6 days for swine dysentery.
    - 25 - 50 ppm for chickens and turkeys for improved weight gain and feed efficiency.
  - 4-Nitro:
    - 188 ppm for weight gain and feed efficiency in chickens and turkeys.
  - p-ureidobenzenearsonic acid:
    - 250 - 375 ppm for prevention and control of blackhead in turkeys.



Arsanilic Acid

Toxicity

- Arsanilic acid and sodium arsanilate:
  - Swine.
    - 250 ppm - Clinical signs appear within 3 - 6 weeks of first feeding.
    - 1000 ppm - Clinical signs appear in 3 - 10 days after begin feeding.
  - Turkeys.
    - Maximum safe level is 300 - 400 ppm.
  - Rat.
    - Newborn LD_{50} oral - 216 mg/kg.
    - Adult LD_{50} oral - over 1,000 mg/kg.
- 3-Nitro:
  - Swine.
    - 250 ppm - Clinical signs develop in 3 - 10 days.
    - 100 ppm - Clinical signs and lesions have been seen within 3 weeks. 75 ppm can cause problems.
    - 187 mg/kg for 30 days fed to swine resulted in paraparesis which progressed to paraplegia. Episodes of incoordination were observed from day 11 which could be illicited by exercise.
  - Dogs - oral LD_{50} is 50 mg/kg.
  - Rat - oral LD_{50} is 155 mg/kg.

Conditions of Poisonings

- Poisoning with either compound is most often a result of misformulation with excessive amounts.
- May result from feeding the high (therapeutic) levels too long.
- Can be due to treating excessively susceptible animals such as those with severe diarrhea or lactating sows.
- Water deprivation for any reason increases susceptibility.
- Use of "3-Nitro" at same levels as arsanilic acid.
- Arsanilic acid and sodium arsanilic are used most and most often are associated with toxicosis. Second in prevalence of use is "3-Nitro" and because of its greater toxicity, persons confusing its dosing level with that of arsanilic acid may misformulate feeds with resultant overdose.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorbed orally or via the skin.
- Arsanilic acid is excreted in the urine, primarily as unchanged compound. Dehydration increases the likelihood and the severity of poisoning. Therefore diarrheas, limited water supply or lactation greatly increase the likelihood of clinical toxicoses. Generally poor absorption from the gut and rapid urinary excretion. Slower excretion from nervous tissue.

Mechanism of Action

- Not the same mechanism as inorganic, alphatic or trivalent organic arsenic poisoning. In these types of poisoning, sulfhydryl (-SH) groups are bound by arsenic, inactivating enzymes with -SH groups important to their structure and function.

- The phenylarsonics do not bind to sulfhydryl groups and, in pigs, are apparently excreted almost entirely unchanged, so that little if any reactive metabolites are formed to exert such an effect.
- Theory (not tested) is that the phenylarsonics may, in some way, interfere with the function of B-vitamins such as B_1 or B_6.
- By whatever mechanism, the phenylarsonics cause demyelination and gliosis (inflammation) in peripheral nerves.
- In functioning ruminants, however, it is theorized that the phenylarsonics may be broken down in the rumen and with sufficient exposure a syndrome similar to inorganic arsenic toxicosis develops (see below).

Signs

- **Swine**.
- Acute (very high dose) phenylarsonic (arsanilic acid) toxicosis.
    - Earliest clinical signs roughened hair coats, diarrhea.
    - Incoordination, ataxia and hyperesthesia developed next.
    - After a few days, lose control of limb movements and animals become paralyzed (posterior paresis to quadriplegia) but, if have access to food and water, will eat and drink. Occasionally head tilt develops. Animals may develop loss of prehensive ability.
    - Arsanilic acid and sodium arsanilate may cause blindness, but this is rarely seen with "3-Nitro" (Roxarsone ®).
    - Reddening of the skin is seen in white animals and sensitivity to sunlight may occur (very characteristic).
    - Signs will completely abate if **acute** (high dose) toxicosis is caught and clean feed is provided within a few days of the onset. If delay in removal from arsanilic acid (e.g., paresis or paralysis present), then demyelination/paralysis can be progressive.
    - Die of thirst, cannot get to water (dehydration).
- Chronic (excessive but not massive overexposure) toxicosis: gradual onset.
    - Goose stepping, knuckling of the hocks.
    - Poor growth, poor feed efficiency.
- Experimental toxicosis of swine with "3-nitro" compounds (187.5 mg/kg, 30 days) produced a syndrome which was slightly different from arsanilic acid toxicosis.
    - Paralysis: mild peripheral and only minimal optic neuropathies.
    - No EEG abnormalities were seen.
    - Erythema of skin present, prolonged discoloration of skin where animal was handled.
    - Arousing animals resulted in urination, defecation, then tremors and episodes of struggling and anxiety evidenced by squealing.
    - Blindness was not detected.
    - Animals continued to eat and drink.
- **Poultry**.
    - Arsanilic acid: anorexia, depression, coma and death.
    - "3-Nitro": Incoordination and ataxia.
- **Cattle**.
    - Arsanilic acid: More resistant than swine but with sufficiently high overdose show signs like those of inorganic, aliphatic or trivalent organic toxicosis (diarrhea, shock, etc.).
- **Dog**.
    - Limited study LD_{50} (approximately 50 mg/kg)-renal hemorrhages.

Lesions

- Ruminants and rats
    - Severe gastrointestinal lesions as in inorganic arsenic toxicosis.
- Swine
    - Gross.
        - Usually no lesions are notable.
        - Erythema of the skin.
        - Muscle atrophy in chronic cases.
        - Abnormally full urinary bladder in some swine.
    - Histopathology.
        - Demyelination of peripheral nerves, optic tracts, optic nerves. Necrosis of myelin-supporting cells and degeneration of axons, with gliosis of affected tracts.

    - These lesions are usually not evident until 6 - 10 days of feeding excessive amounts of phenylarsonics. First the myelin fragments into granules and globules and then, after several days, the axons begin to break down. Lesions are progressive.
    - With "3-nitro" toxicosis, affected swine developed myelin and axonal degeneration of white matter of spinal cord. Degeneration began at 11 - 15 days, was progressive, and corresponded with the development of episodes of extreme incoordination. Peripheral and mild optic neuropathies were also observed. Brain lesions were not observed grossly or on histopathological examination.

Diagnosis

- High morbidity, low mortality.
- Affected swine and poultry often eat and drink but cannot move about due to extreme incoordination (mentally sane).
- Histopathologic findings:
  - Longitudinal sections of long nerves must be examined. In order to achieve this, the nerve must be fixed in a manner which will prevent curling up during fixation. This is readily accomplished by stapling the nerve to a tongue depressor before placing in the fixative. Optic nerve lesions will usually not be evident until 10 days of overexposure and sciatic or brachial nerves will show lesions only after 2 weeks of excessive phenylarsonic treatment.
- If still getting treated feed or treated water prior to killing, 3 - 10 ppm in kidney and liver or 1 - 2 ppm in blood would be diagnostically significant. Likely to be found in urine, but diagnostic concentrations have not been established.
- Usually, because of paralysis, affected animals have not been able to get to feed and since most is excreted within a few days, the kidney and liver arsenic concentrations are often normal.
- Feed, the usual source, is the most worthwhile specimen for diagnostic confirmation. Arsanilic acid at 250 ppm or "3-Nitro" at 100 ppm with concurrent evidence of diarrhea or water restriction tends to confirm the diagnosis.
- Labs can determine arsenic levels in feed and then calculate the amount of arsanilic acid or "3-nitro" present.
- There is also a simple direct spectrophotometric method to detect "3-nitro" in feeds. Contact Iowa State University, Veterinary Diagnostic Laboratory by phone at 515-294-1213.
- Consult with a veterinary toxicologist for interpretation on first few cases.

Differential Diagnosis

Includes nitrofuran or mercury poisoning, Ca/P deficiency, water deprivation, pseudorabies, B vitamin deficiency.

Treatment

- Withdrawal from the source, provision of clean feed and water in such a manner that paralyzed animals are able to eat and drink.
- B-vitamins can be tried, although not tested and shown to be worthwhile.
- Swine showing significant signs may fail to make a complete recovery due to irreversible nerve damage.

Organophosphorus-Induced Delayed Neuropathy (OPIDN)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Cattle, swine, cats, chickens	2 - 4 weeks	Weeks to permanent (common)	

Sources

- This syndrome can result from single or multiple exposures.
- The appearance of clinical signs are delayed for an average of 1 - 2 weeks in many animals and 2 - 4 weeks in man.

- Most, but not all, of the implicated phosphate esters causing OPIDN are insecticides.
- Related compounds (e.g., triarylphosphates) are used in industrial applications such as hydraulic systems, as additives to high-temperature fire-resistant lubricants, and as plasticizers. This class includes triorthocresyl phosphate (TOCP).

Toxicity

- The tendency to cause OPIDN does not parallel the tendency to inhibit acetylcholinesterase. Many OPs have not been associated with OPIDN in spite of their capacity to cause acute toxicosis due to acetylcholinesterase inhibition. Other compounds with comparatively low acute toxicity with respect to cholinesterase inhibition may be potent inducers of OPIDN in the absence of any previous toxicoses. In addition, some compounds such as O-ethyl-0-4-nitro-phenyl phenylphosphonothioate (EPN) are so toxic with regard to cholinesterase inhibition that the significance of their capacity to induce OPIDN is diminished by the small number of poisoned individuals that live long enough to develop the "delayed neurotoxicity" syndrome.
- If death occurs as a result of the induction of OPIDN, it is usually a result of respiratory paralysis or inability to get to water.

Specific Examples

1. Tri-ortho-cresol-phosphate (TOCP).
    - Lubricant, plasticizer, sometimes an adulterant of human foods, beverages.
    - During prohibition was incorporated into Jamaica Ginger, which resulted in an epidemic of "Ginger Jake Paralysis" affecting thousands of humans.
    - At least 6 other TOCP incidents have also occurred, most a result of cooking oil contamination.
    - 7 - 14 day or longer delay before onset. Most other implicated OPs have been associated with an 18 - 21 day lag period before onset.

    Signs (general):

    - Affects motor and sensory neurons.
    - Abnormal sensation in the feet and legs such as tingling and burning.
    - High stepping.
    - Weakness, ataxia.
    - Ascending paralysis, may be flaccid. Gradual progression anteriorly.
    - Effects may be extremely persistent or permanent after exposure terminated.
    - Decreased reflex responses.
    - Muscle atrophy.
    - Severe dyspnea and absence of vocalization may be observed in cattle and pigs.
    - Recovery, if any, is generally slow and often incomplete.
    - Cattle: diarrhea, posterior weakness, ataxia, stiff, difficulty rising, weaving back legs, wide stance. Animals often recumbent 2 - 6 days before death, although occassional sudden death noted. Animals dribble urine.
    - Cattle and pigs: After a few days to several weeks, the peak of the process is reached and thereafter improvement in the functional disturbances begins.
    - Cat: Cats may recover some function, probably dependent upon the extent of lesions.

    Recovery:

    - Mild cases: very slow recovery. Recovery generally more rapid in cat than in man.
    - Severe cases: no recovery.
    - Occasionally can ascend to result in quadraplegia and can cause death, from respiratory paralysis but this is rare. Prevalence:
        - 20,000 human victims of Ginger Jake (Jake Leg) Paralysis.
        - 10,000 human victims from poisoning of Morocco cooking oil which contained 3% mixed cresol phosphates.
    - TOCP is biotransformed via the liver microsome P450 system to the more neurotoxic metabolite saligen cyclic-o-tolyl phosphate.

2. Leptofos (Phosvel ®), produced by Velsicol.
    - Insecticide. Never marketed in the USA although registration applied for.
    - Causes delayed neurotoxicity. Primarily motor neuropathy.
        - Sold in Egypt: caused an epidemic of OPIDN among water buffalo.
    - Also causes mental and emotional dysfunction. Reports of "Leptophos zombies"; name used to describe workers in a leptophos plant in the USA. Workers were also exposed to n-hexane which may have contributed to the development of some clinical signs.
        - Confusion, headache, disorientation, and altered mental and emotional state.
    - Some variation seen between species in ability to metabolize (oxidation, reduction, and dehalogenation reactions) leptofos associated with some variability in susceptibility among species.

3. Other OP insecticides and anthelmintics implicated in delayed neuropathy.
    - DFP.
    - Fenitrothion - Insecticide.
    - EPN - Insecticide: extremely toxic as far as acute cholinesterase inhibition is concerned, OPIDN seen in survivors who are able to survive as a result of therapy.
    - Cyanofenphos - Insecticide (Amaze, Oftanol).
    - Trichlornate - Insecticide.
    - Mipafox - Insecticide.
    - EPBP (S-7)-Insecticide.
    - O-methyl-S-methyl, phosphoroamidate - Insecticide.
    - Trichlorfon - Insecticide and anthelmintic.
    - Carbophenothion (Trithion) - Insecticide.
    - Haloxon - Anthelmintic causes OPIDN in some breeds/strains of sheep.

4. Other organophosphorus compounds implicated in OPIDN.
    - DMPA (Zytron) - Herbicide.
    - Butifos.
    - Merphos - Defoliant.
    - DEF - Defoliant.

5. Other compounds suggested as capable of causing delayed neurotoxicity, not OPs.
    - Diallate (Avadex) - Carbamate herbicide.
    - Sulfallate (Vegadex) - Carbamate herbicide discontinued product.

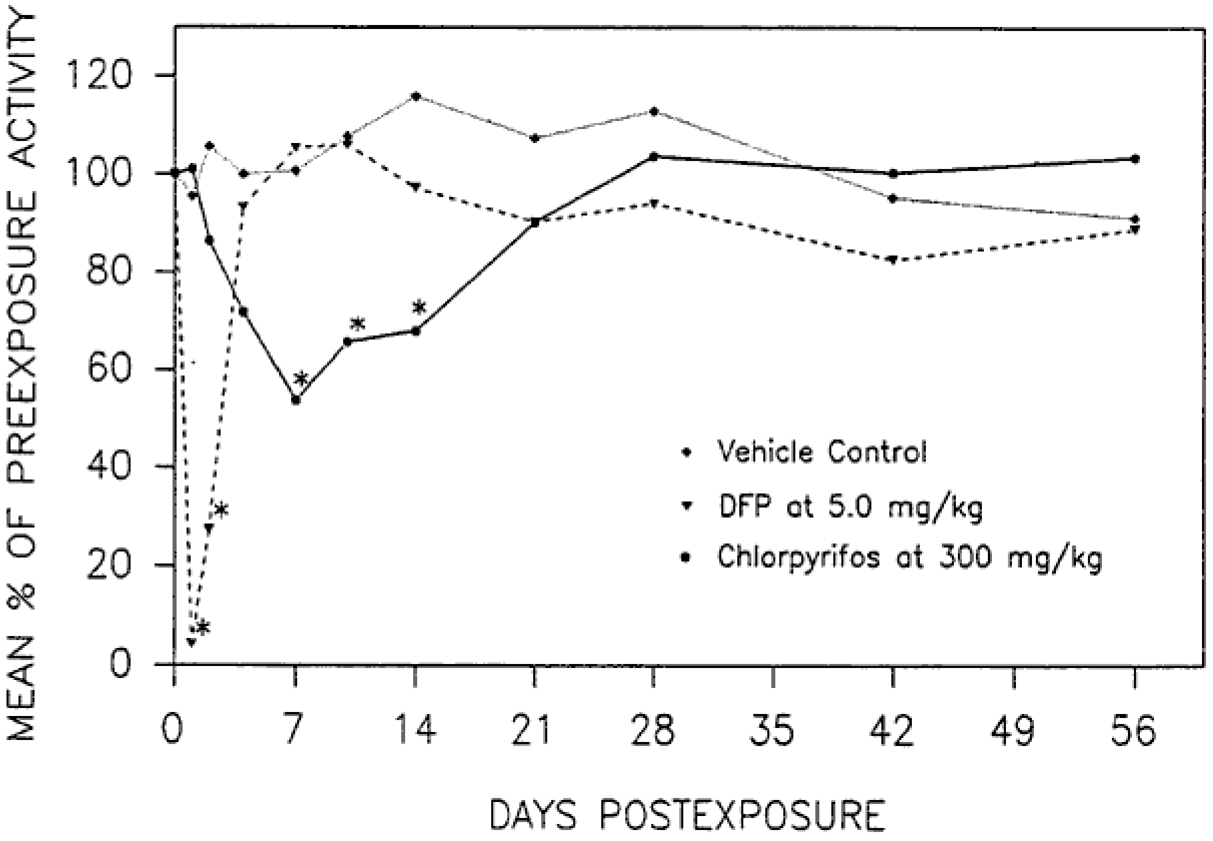
Mechanism of Action (Postulated)

- The development of OPIDN does not correlate with inhibition of acetylcholinesterase.
- The occurrence of delayed neuropathy has a high correlation with the inhibition of an enzyme called neuropathy target esterase (NTE). Maximal inhibition of > 70% at 1 - 2 days after exposure usually is associated with the onset of delayed neuropathy 8 - 14 days later. NTE does not have an identified function in the body. Whether or how NTE inhibition actually leads to OPIDN is therefore unknown. NTE is present in peripheral nerves, lymphocytes, brain, placenta, and several other sites.
- Three mechanisms of action of these OPs have been proposed:
    - A primary toxic effect on the metabolic machinery of the nerve cell perikaryon.
    - A direct action on the axon at certain vulnerable sites without affecting axonal transport.
    - Alteration or interruption of axonal transport.
- Many OP and carbamate insecticides can inhibit NTE but do not produce OPIDN. Besides inhibiting NTE, a compound must be able to undergo "aging" once it is bound to the enzyme before it will produce OPIDN.
- Inhibitors of NTE can be put into 2 groups:
    - Group A (phosphates, phosphoramidates, and phosphonates) are axonopathic, can "age" and are therefore potentially neurotoxic.
    - Group B (sulphonates, phosphinates, and carbamates) are not axonopathic, will bind to esterase, do not age and can therefore be protective.
- The essential difference between these 2 groups is the ability of Group A compounds to undergo aging. Prior administration of a compound from Group B can be protective against the delayed neurotoxic effects of subsequently administered Group A compounds.

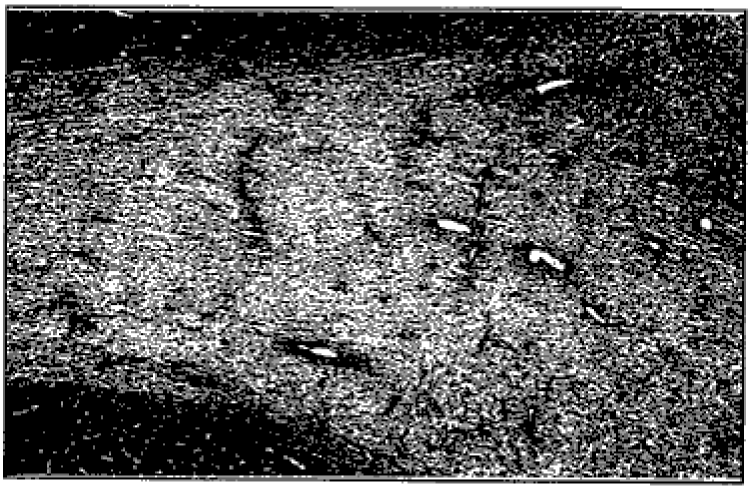
Species Sensitivity (Varies at Least with Some Compounds)

Susceptible Species

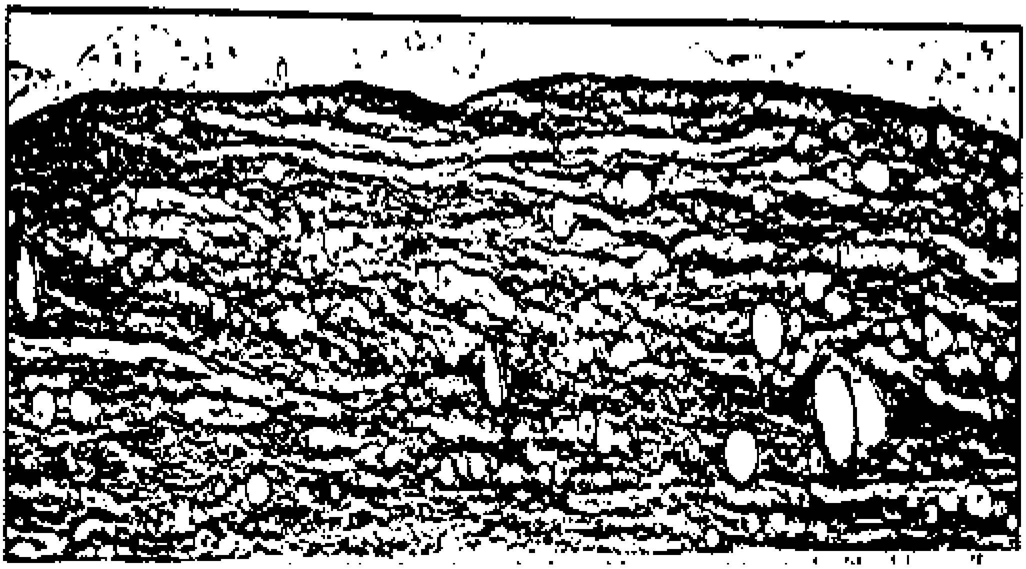
Chicken, duck, turkey, horse, cow, sheep, pig, dog, cat, baboon, rat, and man.



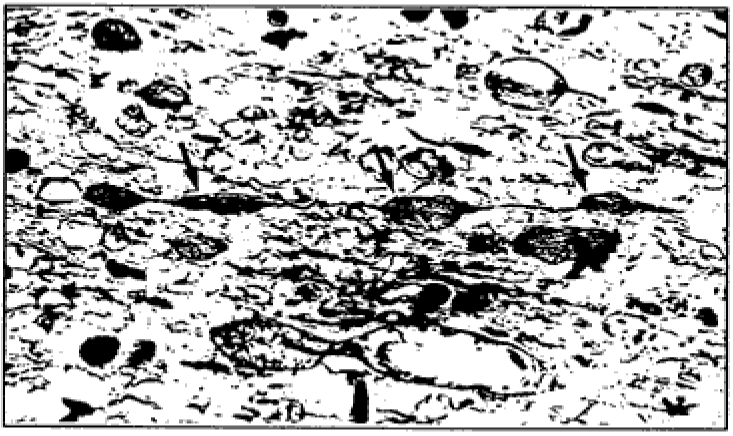
Mean percent inhibition of lymphocyte neuropathy target esterase (LNTE) activity in cats exposed to a single, im dose of corn oil (vehicle control), DFP (positive control), or chlorpyrifos. Data points are expressed as a percentage of the group's mean predose LNTE activity. The mean (± SD) predose LNTE activity for the corn oil, DFP, and chlorpyrifos groups were 8.97 ± 1.50, 10.16 ± 1.83, and 9.48 ± 2.61 nmol of phenyl valerate hydrolyzed/min/mg of protein, respectively. *indicates significantly different ($p<0.05$) from vehicle controls.



Cerebral cortex (frontoparietal lobe) from a cat treated with 300 mg of chlorpyrifos/kg of body weight. Vacuolar change confined to white matter. H & E, x 35.



Longitudinal section of lumbar (L_4) spinal cord from a cat treated with chlorpyrifos at 300 mg/kg of body weight. Vacuolar change with associated myelin debris and macrophage infiltration. H & E, x 215.



Higher magnification. Multifocal axonal swelling (arrows). Bodian's stain, x 1060.

Nonsusceptible Species

- Mouse, rabbit, guinea pig, hamster, and gerbil.
- The adult hen (greater than 180 days of age) appears highly sensitive and is used in OPIDN screening of OPs. For an unknown reason, young chickens and probably the young of other species are more resistant to OPIDN.
- Suffolk sheep appear genetically predisposed (at least to Haloxon).
- Humans are extremely sensitive.

Lesions

- Characterized as a central-peripheral distal axonopathy (axons injured first, myelin damage is secondary).
- Histopathological analysis requires longitudinal section of spinal cord and peripheral nerves (staple nerves to tongue depressor during fixation).
- Clumping of myelin, foamy appearance of myelin, broken axons (axonal degeneration).
- The distal nerves of the peripheral nervous system are affected earlier and more severely than proximal fibers "dying-back polyneuropathy".
- Large diameter fibers appear more affected than small diameter fibers.
- Lesions are symmetrical and involve both sensory and motor pathways. Axon degeneration occurs largely in spinal cord tracts and peripheral nerves in hindlimbs.
- Demyelination occurs as a secondary event after the primary axonopathy.

Treatment

- No effective therapy is recognized.
- Treatment with atropine and oximes (2-PAM) minimize initial development of signs related to cholinesterase inhibition but do not prevent the development of OPIDN.

Lathyrus spp. - Vetchlings

(Equine Cystitis-ataxia and Teratogenesis Syndromes)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Horses, cattle	10 days to 2 months	Weeks to permanent damage	

Source

- Most reports of serious lathyrism have come from Europe, Northern Africa, Russia and India. These outbreaks, which are now generally of historical interest, arose primarily from conditions of poverty and drought in which people were forced to subsist on a diet composed largely of *Lathyrus* sp. seeds. Large quantities of these seeds in the diet can produce a paralytic syndrome in man and livestock.
- Toxic species of *Lathyrus* in the USA and Canada include:
    - *L. hirsutus* (Caley pea, wild winter pea, singletary pea).
        - This plant has legume fruit pods, 1 - 1.75 inches long, 1/4 inch across, flat, hairy, many seeded, splitting in two halves which become tightly twisted when dry. Used as an annual winter forage or cover legume in the southern USA, California and Oregon.
    - *L. incanus* (wild pea).
        - Native to the dry, sandy plans of Nebraska, Colorado, and Wyoming.
    - *L. pusillus* (singletary pea).
        - Winter cover crop in the Gulf states, naturalized in area from Texas to Kansas to Florida to North Carolina.
    - *L. sylvestris* (everlasting pea, flat pea).
        - Coarser, persistent perennial, with 2.5 inch (6 cm) long, 0.5 inch (1.25 cm) wide pods. Naturalized in the northern USA and southern Canada.
    - *L. odoratus* (sweet pea).
        - This popular climbing vine is a favorite among gardeners for its sweet-smelling blossoms. The clusters of flowers may be white, pink, lavender, red or purple. The leaves are slightly elongated ovals with pointed tips, appearing in pairs on the winged green stems. Small, hard, green peas about 1/4 inch (0.6 cm) in diameter are borne in green seed pods.

Susceptible Species

- Different species of livestock vary considerably in susceptibility. The horse is particularly sensitive to the toxic principle and is most often poisoned.
- A diet of exclusively *L. sativus* seeds brings on signs in the horse in approximately 10 days. When fed 1 or 2 quarts of seeds per day, signs are delayed in onset for 2 - 3 months and may appear a month or more after withdrawal of the seeds from the diet.

Toxic Principle (in Sweet Pea)

- The toxic principle of the sweet pea is beta-(gamma-L-glutamyl)-aminopropionitrile. It is localized primarily in the pea or seed of the plant. Once ingested this compound may be converted *in vivo* to beta-aminoproprionitrile, which appears to be the substance responsible for the toxic effects.
- Neurotoxin is heat labile and can be destroyed by cooking.
- When the seed is ingested chronically, as in India where it makes up part of the native diet, it causes skeletal deformities due to inhibition of cross-linking during the formation of collagen. In the development of vascular walls, elastic fiber formation is inhibited, thus lowering the resistance to

vascular wall stretching. The end result is a predisposition to vascular aneurysms. During pregnancy, the developing fetus is especially sensitive to the poison.

- Primary neurotoxin in *L. sativus*, ß-N-oxalyl-L-a-g-diaminoproprionic acid (ODAP), appears to cause direct neurotoxicity. Signs of neurolathyrism in man include muscular rigidity and paralysis of legs.

Clinical Signs

- Two forms of lathyrism are recognized: neurolathyrism and osteolathyrism.
- The acute toxicity of sweet pea ingestion is manifested as a paralytic syndrome; although the pea has to be consumed in rather large quantities before clinical signs develop. Other signs may include a slow, weak pulse, depressed and weakened respiration, and convulsions.

Signs in Cattle *(L. Hirsutis)*

- Osteolathyrism predominately affects livestock.
- Lameness in cattle may appear between the 3rd and 5th day of consumption when seeds are present at the time of poisoning. Lameness may rarely be severe. In experiments on pasture, and in feeding forage, no lameness occurred when the seeds were absent.

Signs in Horses

- Weight shifted to front legs.
- Hind legs held forward and a hopping gait.
- Seem normal when in a recumbent position.
- When get up, pain is associated with locomotion and may appear as if "tied up" due to stiffness in hindquarters.
- Sometimes the head is held low.
- Paralysis of recurrent laryngeal nerve leading to dyspnea and roaring.

Signs in other Species

L. hirsutus - Experimentally, reproductive problems (chickens) and lameness and skeletal abnormalities (swine and chickens) have been reported.

Specific Syndromes

- *L. incanus*.
    - In Wyoming, *L. incanus* has been suspected of producing lameness in horses on range.
- *L. pusillus*.
    - Reported to cause livestock poisoning, experimental lameness and bone deformities in chickens.
- *L. sylvestris*.
    - Experimentally produces characteristic nervous signs of hyperexcitability, convulsions, and death without skeletal lesions.

Lesions

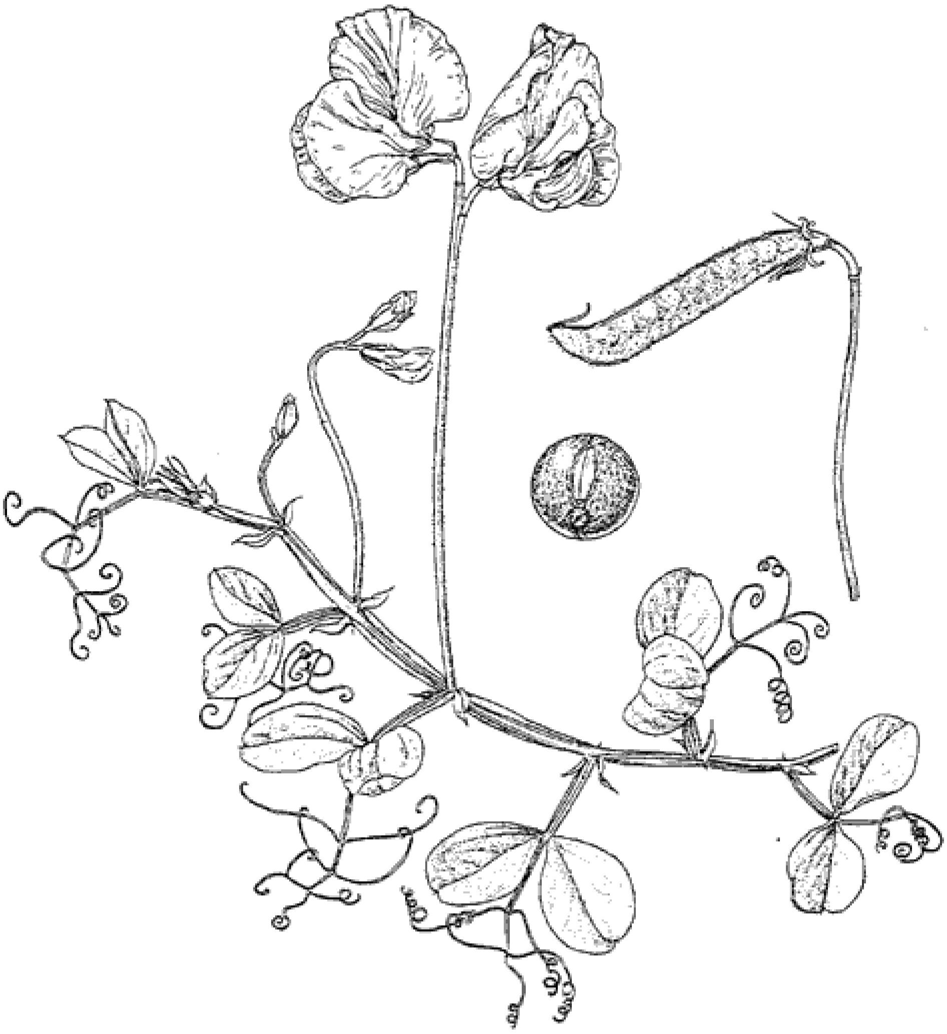
Neuronal degeneration in the spinal cord and nerves to the hind legs (neurolathyrism).

Prognosis

- Some animals make a full recovery.
- Others are chronically affected: for example, 2 years after *Lathyrus* toxicosis some affected horses exhibit stringhalt-like signs (incoordinated when forced to back up; legs stay flexed too long).

Treatment

If large quantities of the seed have been ingested, induce emesis and perform gastric lavage. Administer activated charcoal and a saline cathartic. Thereafter, symptomatic and supportive therapy is indicated.



Sweet Pea - The conspicuous and colorful butterfly-shaped flower, the pinnately divided leaves with tendrils, and the hairy seed pod and enlarged seed (upper right) characterize this colorful garden forb.

Sorghum spp. - Hybrid Sudan (Equine Cystitis-ataxia and Teratogenesis Syndromes)

***Sorghum vulgare*, var. sudanesis** - Sudan grass

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Horses	Average 8 weeks	Often permanent neurologic damage; secondary urinary tract infection may be lethal; also teratogen in horses	

Source

- Sudan grass is a member of the *Sorghum* spp. which are most often associated with cyanide or nitrate toxicoses.
- In horses, especially females, a syndrome of cystitis and ataxia has been associated with the consumption of Sudan grass in the southwest United States. Observed in Texas, Oklahoma, New Mexico, Arizona, California, Kansas, and Colorado.

    - Area incriminated most definitely is between Corpus Christi, Texas, and Fort Dodge, Kansas, and 300 miles either side of a line connecting these two cities.
    - All breeds of horses are involved.
- Similar ataxia-incontinence syndrome reported in horses and cattle of Australia grazing sorghum.

Toxic Principle

- Believed to be the lathyrogenic agent, beta-cyanoalanine.
- May also contain cyanogenic glycosides and nitrate in toxic amounts (which cause other syndromes).

Toxicity

- Associated with grazing of hybrid Sudan pastures. Grazing periods varies from 1 week to 6 months, average period 8 weeks in 1 report.
- Not associated with eating the cured hay from the pastures. **Freshly cut** hay has been implicated.
- Poisoning occurs from July to December or until frost kills the plant. Generally occurs during seasons of high rainfall. Young rapidly growing plants most commonly involved.
- Fertilization of the pasture seems to have no effect on toxicity of the Sudan grass.

Signs

- Posterior ataxia and incoordination in the rear legs is the most commonly observed clinical sign. May appear normal when standing but when forced to move may almost drop to the ground with one or both legs flexed. Horse may then recover and walk off more or less normally.
- When backed may sit or fall down into lateral recumbency. Flaccid paralysis of hind limbs may develop within 1 day of onset of ataxia.
- May weave as each foot is placed on the ground and may be confused with equine wobbler disease.
- Frequent opening and closing of the lips of the vulva (winking) and constant or frequent dribbling of urine (urinary incontinence).
- Urine scalding and contamination with associated irritation and exudation of the area ventral to the vulva and to a lesser degree the rear legs down to the hocks. Yellow putty-like sediment (urine odor) is deposited in skin.
- Mares may appear to be in constant estrus. Usually due to constant irritation of the urethra and vagina due to passage of urine and exudate from a constantly full urinary bladder.
- Cystitis results from sediment accumulation, urine stasis, and bacterial over growth. In general, cystitis is relatively uncommon in the horse.
- Males may squirt urine and the penis may be partially relaxed. With chronic toxicosis may constantly dribble urine. Partial alopecia on ventral abdomen.
- Dribbling urine in both sexes increased if animal is forced to move suddenly.
- Normal body temperature, pulse and respiration rates, appetite, and maintenance of body condition unless pyelonephritis occurs.

Teratogenesis

- Fetal malformations may occur when mares graze hybrid sudans during the 20th - 50th day of gestation. Foals may be born with extreme flexion of the joints or ankylosis. May result in dystocia.
- Abortions may also result.

Clinical Pathology

- Leukocytosis and lymphocytosis.
- Commonly see a normal urine pH of 8 and normal specific gravity of 1.030. Proteinuria may be present.
- Sediment: blood, epithelial cells, many bacteria, large numbers of calcium carbonate crystals. Hyaline and granular cysts present in some sediment exams.
- Urine culture: *E. coli* most commonly isolated in combination with *Corynebacterium* spp., *Staphylococcus* spp., *Proteus vulgaris*, and/or *Pseudomonas aeruginosa*.

Lesions

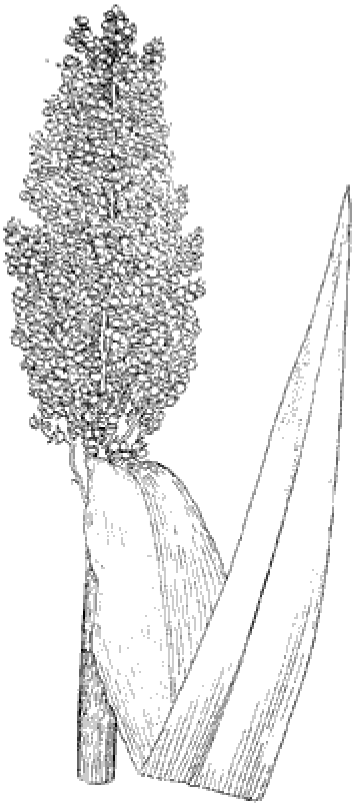
- Urinary bladder - Cystitis with markedly thickened bladder wall (2.5 - 3.5 cm) with large volumes of urine present. Mucosa and ureters may be hyperemic. Bladder contains amorphous, semisolid yellow deposit (calcium carbonate). Bladder mucosa occasionally ulcerated.
- Vagina - Reddening and sometimes coated with sediment.
- Kidneys - Pyelonephritis is sometimes present and may be the cause of death.
- Thoracic, lumbar and sacral spinal cord: neuronal degeneration and mild myelomalacic change in these areas of the cord.
- Arthrogryposis in foals (especially contracted joints).
- Histologic findings include acute, occasionally necrotizing cystitis. Degeneration of axons and demyelination in cervical, thoracic, lumbar, and sacral spinal cord segments.

Prevention

Keep horses off Sudan or Hybrid Sudan pastures.

Treatment

- Generally unsuccessful; antibiotics, nitrofurans, acidification of the urine and DMSO have all been tried. Changing of the diet from hay to grain and the use of antibiotics may provide temporary relief, but the syndrome generally recurs in 1 - 2 weeks after the therapy is stopped. Once the animal exhibits significant incoordination or dribbling or urine, complete recovery seldom if ever occurs.
- **Note** - A similar contracted foal syndrome in Europe has been described, but no connection with sudan grass or other causative agent has been made.



Sorghum - fruit cluster with leaf.

***Acacia* spp.**

Acacia berlandieri - Guajillo (pronounced Wah-hee-O)
A. georginae - Gidyea
A. greggi

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Sheep, goats	6 - 9 months	Months; may be lethal; up to 50% may die	

Family - *Leguminosae* (pulse or bean family)

Introduction

- Cause of "limberleg" or "Guajillo wobbles".
- Chronic ingestion of large amounts of the leaves and fruit (15 times the animal's weight) has been associated with toxicosis.
- This plant is considered a valuable forage species in some areas.
- Drought may result in this plant being the only forage available.
- Losses may be negligible during years of average rainfall.
- N-methyl-beta-phenyl-ethylamine hydrochloride administration (orally) to sheep at 375 mg/kg caused clinical toxicosis.
- Goats cannot be successfully maintained on ranges where Guajillo is present.

Habitat

- *A. berlandieri*: Texas, especially in the southern part of the Edward's plateau and Trans-Pecos (Chisos Mountains) areas. Rangelands.
- *A. greggi*: Limestone areas of Arizona; other areas?
- *A. georginae*: Queensland, Australia.
- *A. nilotica* subsp. *kraussiana*: South Africa.

Toxic Principle

- *A. berlandieri*
    - Sympathomimetic amines.
    - Tyramine, N-methyl tyramine.
    - N-methyl-beta-phenylethylamine.
- *A. georginae*.
    - Fluoroacetate.
- *A. greggi*.
    - Cyanide.

Toxicity

- General (*A. berlandieri*).
    - Oral lethal dose is approximately 450 mg/kg.
- *A. georginae*.
    - Six to 9 months on a diet containing this species is generally sufficient to produce toxicosis.
    - Mortality is generally low, but may reach 50% during drought years.
- *A. nilotica* subsp. *kraussiana*.
    - In goats the lethal dose is 30 g/kg, but 5 g/kg can be harmful if fed over long periods.
- *A. greggii*.
    - Potentially lethal in the limestone areas of Arizona.
    - Cases generally appear in the Fall or at the first frost.
- **Note -** Remainder of section pertains exclusively to Guajillo (*A. berlandieri*).

Description

- *A. berlandieri*

    - Plant - Perennial, pubescent shrub or small tree; 3 - 14 feet tall.
    - Stem - Leaf branches, 3 - 9 pairs.
    - Leaves - Alternate, twice pinnate; leaflets 3 - 6 mm long, numerous, 24 - 45 pairs, oblong-linear, oblique, acute, veiny with few or no prickles.
    - Flowers - White to yellow, sweet scented, axillary, leguminous, in dense groups, in globose heads.
    - Fruit - Legume, flattened, 4 - 6 times as long as wide; somewhat thickened margins, obvious at maturity, scattered among the foliage.

Mechanism of Action

Proposed mechanism of action is that the sympathomimetic amines of *A. berlandieri* compete for and then inactivate monoamine oxidase.

Susceptible Species

Sheep, goats.

Signs (*A Berlandieri*)

- General.
    - Clinical signs develop after 6 - 9 months ingestion as the sole diet.
    - Ataxia develops in the hind legs and occasionally the front legs.
    - Rubbery appearance of rear legs is first noticed when animals are forced to move.
    - Animals may get excited and become prostrate.
    - Generally animals remain alert and retain their appetite.
    - Nevertheless, many deaths on the range may be due to starvation and thirst.
- Sheep.
    - After grazing almost exclusively on Guajillo, sheep sometimes develop locomotor ataxia referred to as limber leg.
    - Stilted gait of the rear limbs, side to side swinging of the hips.
    - Forelimbs may then be affected.
    - Signs become exaggerated, animals are forced to move about.
    - Prostration.

Diagnosis

Identification of Guajillo, evidence of prolonged consumption, appropriate clinical signs.

Treatment

- Remove animals from access to the plant.
- Feed prostrate animals.
- Recovery usually occurs in a few months.

Prevention

- Do not allow animals to graze exclusively on Guajillo.
- When poisoning does occur, supplement feed and reduce stocking rates.
- Guajillo may be killed with herbicides.

Karwinskia humboldtiana - Coyotillo

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Cattle, sheep, goats, horses	Weeks to months	Weeks to permanent damage	

Synonyms - Buckthorn, tullidora, capulin tullidor, capullincillo, cacatsi

Habitat

- Southwestern Texas into northwestern Mexico and Baja California.
- Rangelands, gravelly hills, canyons, river valleys, along arroyos.

Description

Spineless woody shrub or tree, 1 - 7 m tall. Leaves are veined opposite, petioled and eliptical to ovate (3 - 8 cm long) and have prominent veins. Small flowers are yellow-green, clustered in leaf axils with 5 sepals and 5 petals. Fruits (drupes) are ovoid, brownish-black or dark purple at maturity, 1 cm in length, is a several seeded berry, in the axils of the leaves. May flower at any time of year depending on weather. Fruits most often present from November to February.

Toxic Principle

Unknown. Contains anthracenones as well as a cumulative neurotoxic C-15 polyphenol.

Toxicity

Seeds (fruit) are the most toxic followed by the leaves. Toxic dose of whole fruit on a dry weight basis varies from .05 - 0.3% of body weight. For green foliage, this figure is 15 - 20% of the animals weight. Paralytic condition is caused by fruits not by the leaves. Winter season is most dangerous due to lack of good forage. Poisoning may result from a single feeding; however, most toxicoses occur after several days or even weeks of exposure.

Mechanism of Action

Unknown, but one component reportedly uncouples oxidative phosphorylation.

Susceptible Species

- Cattle - goats, sheep, and horses have experienced naturally occurring toxicosis.
- Sheep - 0.2% of the body weight of the ground fruit may be lethal. Similarly 20 - 25 lb of the leaves may be required to cause death. Sheep are the most commonly affected species.
- Frogs, snakes, chickens, rats, rabbits, chickens, and possibly dogs are susceptible experimentally.
- Children and soldiers-have been poisoned by eating the berries. In one outbreak, 10% of the affected soldiers died and others were still disabled 14 months after exposure. Recovery in man does occur but may take over 1 year.
- Snow monkeys (*Macaca fuscata*).

Signs

- Unthriftiness, depression, weakness, trembling, hindlimb incoordination, hypermetric respiratory distress, and dyspnea. As condition progresses, forelimbs may become affected.
- Paralytic condition affecting especially the hindquarters.
- "Limberleg", of cattle and sheep. Severely poisoned animals may jump and move backwards.
- Goats may walk on their knees.
- There is a lag period prior to appearance of signs from a few days to several weeks. Appetite remains normal. Most severely poisoned animals do not recover.
- "Bulbar weakness", respiratory, and possibly cardiac failure may lead to death.
- Reduced conduction velocities in affected nerves.
- The chronic wasting condition produced by the leaves is associated with signs of nausea, progressive weakness and death.

Lesions

- The motor paralysis is attributable to a segmental demyelinating neuropathy. Schwann cells swell and myelin laminae split at the intraperiod lines with formation of myelin vacuoles.
- Demyelination is more prominent than axonopathy. Chromatolysis, especially in the anterior horn cells of the spinal cord (probably secondary to peripheral damage), with time remyelination and axonal regeneration may occur. Swollen axons in white matter of cerebellum of goats.
- There may also be a lymphadenopathy, and small hemorrhages on the heart.
- Inflammatory lesions may be present on the mucosa of the stomach and intestines. In lethal cases, severe pulmonary edema tends to occur, and there may be microscopic degeneration of skeletal and cardiac muscle. Mild toxic nephritis and centrilobular hepatic necrosis and fatty change has been described. Demyelination of posterior spinal cord.
- Elevated CPK and SGOT due to indirect muscle damage.

Prevention

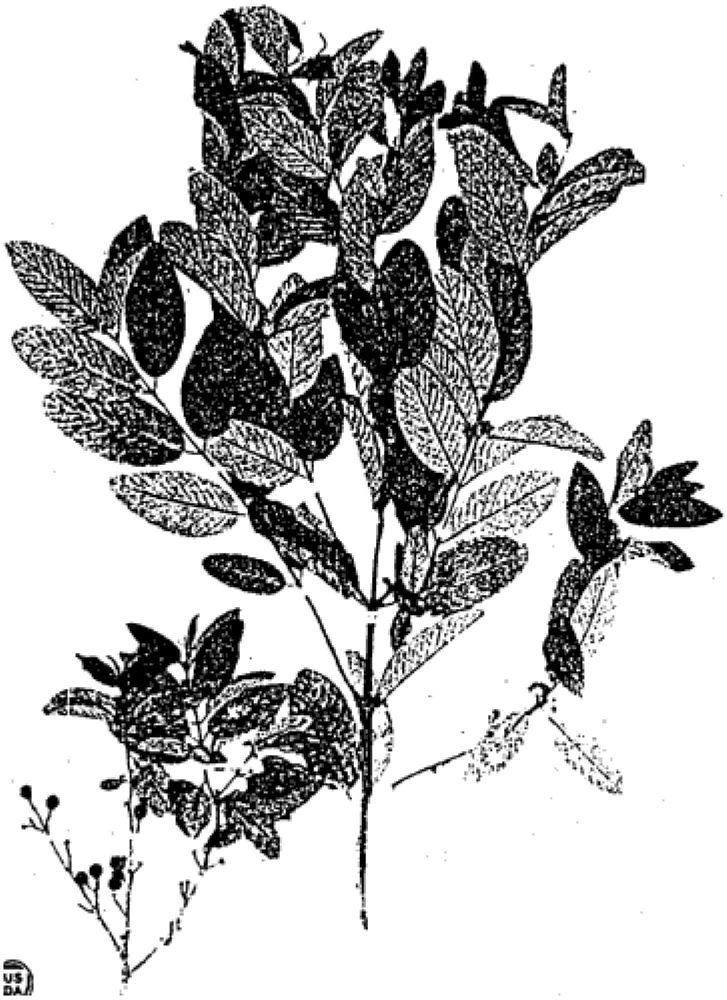
Avoiding exposure of unfamiliar animals to the plant and do not overstock ranges.

Differential Diagnosis

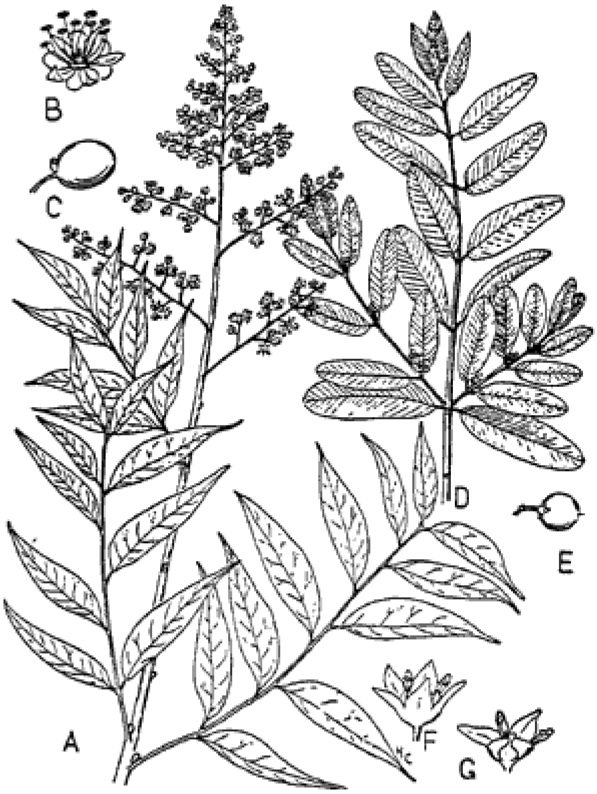
Acacia (also produces condition called limberleg). Syndrome is similar to triaryl phosphate (TOCP) toxicosis.

Treatment

Daily administration of thiamine has been reported to be of value in humans.



Coyotillo (*Karwinskia humboldtiana*) - Showing the leaves and fruit.



Sapindus Drummondii, Soapberry - A, flowering shoot; x 1/3. B, flower; x 3. C, fruit; x 1/3. *Karwinskia Humboldtiana*. Coyotillo. D, flowering shoot; x 1/3. E, fruit; x 1/2. F-G, flower; x 3.

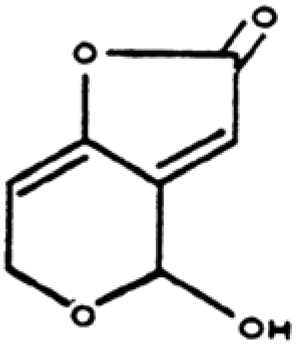
Citreoviridin and Patulin : Mycotoxins Causing Paralysis

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Paresis or Paralysis
Citreoviridin (Mycotoxin)	Cattle	(Importance of this mycotoxin in the field has not been well established)		
Patulin (Mycotoxin)	Cattle	(Toxicosis is very rare)		

Citreoviridin

- A *Penicillium* spp. mycotoxin sometimes found in rice (and probably other substrates).
- Can cause ascending paralysis with convulsions and respiratory paralysis resulting in respiratory arrest.
- Cardiovascular and respiratory failure may occur 3 days after the initial onset of paralysis.

Patulin



- Mycotoxin produced by *Penicilium* spp., *Aspergillus* spp., *Byssochlamys fulva*, and *B. nivea*.
- Produced in apples, pears, grapes, barley, malt, rice, and wheat straw. Detectable to 1 mg/l apple juice.
- Unstable if mixed with wheat flour, ground sorghum or ground wet corn; and unstable if SO_2 (sulfur dioxide) is used as a preservative in apple products.
- Fermentation with *Saccharomyces* spp. (as is used in cider production) also inactivates patulin.
- Cattle have reportedly exhibited an ascending paralysis of motor nerves with convulsions, excitement and cerebral hemorrhage.
- Lesions may include pulmonary and cerebral edema, ascites, congestion of liver, spleen, and kidneys in addition to the effects described above.
- Inhibitor of RNA polymerase.
- LD_{50} mice (SC) 8 - 15 mg/kg, oral LD_{50} mice 35 - 48 mg/kg.
    - Mice displayed restlessness, heavy labored breathing, and convulsions.

Note - The importance of either of these mycotoxins (citreoviridin or patulin) in the field has **not** been established.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Paresis or Paralysis
Avidin in raw egg white (causes biotin deficiency), however, egg yolks are rich in biotin				
Locoweed (*Astragalus* and *Oxytopis*) (Miserotoxin = 3-nitro compounds)	(See Toxicants with Mixed Effects on the Central Nervous System)			
Solanum dimidiatum	Cattle	Unknown	Chronic to permanent damage; potentially lethal	
Cycad palms (*Cycas* or *Zamia*)	Herbivores, dogs, swine	Hours to a few days	Weeks to permanent damage; often lethal	
Lolitrem B from *Acremonium lolii* in perennial ryegrass (*Lolium perenne*)	Sheep, cattle, sometimes horses	Chronic	Chronic; rarely lethal	
Tetrodotoxin (sodium channel blocker) in: - Puffer fish (*Tetraodon* and *Fugu*) - California newt (*Taricha*; a salamander) - European newt (*Tariturus*; a salamander) - Unk (*Bombia*; a salamander)	Pet animals (carnivores)	Minutes to hours	Days to several weeks	
Saxitoxin and neosaxitoxin (sodium channel blockers). Responsible for paralytic shellfish poisoning-from cocles, mussels, clams. Name derived from the Alaskam butter clam, *Saxidomas giganticus*). Poisoning is much more commonly a result of eating oysters. All acquire the toxin from the dinoflagellate, *Gonyaulax* spp., usually	Pet animals (from eating shellfish); All species (from drinking blue-green algae in surface waters)	Minutes to hours	Hours to months. Human cases often reported; potentially lethal	

evident as "red tides". The same toxins are produced by certain strains of at least 2 species of blue-green algae (*Aphanizomenon flos-aquae* and *Anabaena flos-aquae*)			
Ciguatera (ichthyosarcotoxin, that causes sodium channels to stay open) in red snapper, barracuda, and other warm water, carnivorous, marine fish that bioaccumulate the toxin synthesized by marine benthic dinoflagellates, e.g., *Gambierdiscus* spp. Ciguatera causes neurologic, gastrointestinal, and cardiac dysfunction.	Pet animals	Hours to two days	Days to weeks; rarely lethal
Sulfonamides (cause peripheral neuritis)	All species esp. chickens and cattle	Days to weeks	Weeks to permanent damage; potentially lethal
Mephenesin	Small animals	Hours to days	Hours to days; unlikely to be lethal
Selenium (*Lycopersicon*) (may also contain toxic amounts of nitrate)	Swine; other species	Seven weeks to months	Damage may be permanent; potentially lethal

- Mephenesin
- Tetrodotoxin (sodium channel blocker)
    - Puffer Fish (Tetraodon and Fugu)
    - Poison Dart Frogs-Central and South America
    - California Newt (*Taricha*) (a salamander)
    - European Newt (*Tariturus*) (a salamander)
    - Unk (*Bombia*) (a salamander)
- Saxitoxin and Neosaxitoxin (sodium channel blocker)
    - in Paralytic Shellfish Poisoning - From cockles, mussels, clams. (Especially the Alaskan butter clam, *Saxidomas giganticus*) and especially oysters - All from the Dinoflagellate (*Gonyaulaux* spp.). Also contain the similar acting neosaxitoxin.
    - in Red Tide. Same Dinoflagellate in Fishes
    - in Blue-Green Algae (Aphanizomenon) - May contain both saxitoxin and the similar acting neosaxitoxin
- Ciguatera
    - Ciguatera is the neurologic, gastrointestinal, and cardiac syndrome produced by ciguatoxins, which are oxidative metabolites of gambiertoxins. The latter are produced by the benthic dinoflagellate *Gambierdiscus toxicus*.
    - The toxins bioaccumulate in food chains. People and pet animals may be exposed through consumption of warm-water, carnivorous, marine fish, such as red snapper and barracuda.
    - The mechanism of action of ciguatoxins is to cause sodium channels to stay open.
- Avidin in raw egg white (causes biotin deficiency), however, egg yolks are rich in biotin.
- Sulfonamides (peripheral neuritis) (See Toxicants that Affect the Kidneys)
- Selenium (subchronic selenosis in swine (See Toxicants Causing Skin Effects other than Photosensitization)
- Cycad Palms (See Poisonous Plants that Affect the Liver)

Toxicants that Primarily Cause Respiratory Paralysis

V. Beasley

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Hydrogen Sulfide (H_2S)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Primarily Cause Respiratory Paralysis
Swine, all species	Minutes to 2 hours	Few hours, generally animals in confinement are affected; rapid death occurs; major hazard to farm workers	

Characteristics

- Colorless.
- Heavier than air (sp. gr. 1.189).
- Flammable and explosive.
- Characteristic odor of rotten eggs.
- Produced by anaerobic bacteria during the decomposition of protein and other sulfur containing organic matter.

Source

- Liquid manure holding pits.
- Continuously produced and retained within the pit (solubilized in the liquid contents rather than free as a gas).
- The concentration of H_2S found in most closed animal facilities is generally in the area of 10 ppm, a nontoxic concentration.
- Agitation of the waste slurry, for example: resuspending solids prior to pumping the contents out or restarting units which were intended to continuously circulate water through the pit and have failed, will cause the sudden release of hydrogen sulfide producing concentrations of 100 ppm or greater.
- Another source of hydrogen sulfide is in deposits of natural gas, crude oil and some coal deposits. Sour gas (oil wells) is a mixture of aliphatic and aromatic hydrocarbons, hydrogen sulfide, and other volatile sulfur-containing compounds. Hydrogen sulfide is considered the most toxic constituent.
- Other industrial sources include hydrogen sulfide as a by-product, waste material, and H_2S leaks during its use or storage as a reactant in chemical synthesis.
- Other sources of sulfer, even oxidized forms such as sulfate in water or gypsum are thought by some workers to be reduced in the rumen to form H_2S and thus to induce chronic hydrogen sulfide toxicosis.

Toxicity and Clinical Signs

- Humans can detect low concentration such as 0.025 ppm which are nontoxic.
- Concentrations greater than 200 ppm hydrogen sulfide paralyze the olfactory apparatus eliminating the normal avoidance responses of exposed humans.
- At concentrations of above 300 ppm, the gas is a potentially imminent threat to life.
- Between 500 and 1000 ppm the effects of hydrogen sulfide may include permanent damage to the nervous system. Apnea can occur.
- At 1500 ppm, the course of events is the same, except the reaction is more intense.
- At greater than 2000 ppm, breathing becomes paralyzed after a breath or two, due to a direct paralyzing effect on the respiratory center. Generalized convulsions frequently occur at this time. Breathing is not reestablished in unassisted patients although temporarily the heart will continue to beat until the asphyxia results in death.
- In the presence of artificial respiration, or in the less severely affected animal which has not yet become apneic, the gas can be effectively eliminated from the body if sufficient exchange with uncontaminated air takes place.
- Ocular and respiratory tract irritation can occur. Threshold for serious eye injury is 50 - 100 ppm.

- Animals may exhibit brief excitement followed by listlessness decreased responsiveness to stimuli and inability to rise.
- Sometimes animals show mental derangement ("crazy behavior") and irritability.
- Secondary pulmonary and/or ocular bacterial infections may occur in affected surviving animals.
- Chronic long-term effects in humans include neurological, pulmonary, cardiovascular, and ocular disabilities.

Mechanisms of Action and Clinical Signs

- Sulfide ions act as direct cytotoxins, bind to cytochrome oxidase within mitochondria, and block electron transport. Syndrome differs from cyanide (another cytochrome oxidase inhibitor).
- Hydrogen sulfide is an irritant gas causing local inflammation of the moist mucous membranes of the eye and respiratory tract. The entire respiratory tract is irritated, but the deeper structures of the lung are irritated the most. This can result in pulmonary edema.
- Although the heart and skeletal muscles may be affected, the primary effect is on the chemoreceptors of the carotid body, which are stimulated leading to rapid breathing and secondary depletion of carbon dioxide (hypocapnia) from the blood. This in turn results in a period of respiratory inactivity (apnea). If depletion of CO_2 does not proceed too far, the subsequent accumulation of carbon dioxide may again stimulate respiratory exchange. If however, spontaneous recovery does not occur and artificial respiration is not immediately provided, death from asphyxia is the inevitable result.

Lesions

Animals dying as a result of hydrogen sulfide toxicosis are generally cyanotic and may exhibit pulmonary irritation and possibly pulmonary edema.

Prevention

- Manure pits should not be agitated without removing the animals from the enclosed area. If this cannot be done, maximum air exchange should be present in the form of widely opening the building and using the full power of fans present, regardless of the time of the year. When mechanical fans are not present, procedures which may increase hydrogen sulfide release from animal wastes should not be performed until a stiff breeze will provide adequate exchange of air.
- Persons should not enter building with suspected hydrogen sulfide contamination due to the imminent hazard present to human health. Pumps should be turned off and the building thoroughly ventilated until the gases have had time to escape. Manure pits and septic tanks should not be entered, even when empty.
- Additional procedures for the avoidance of human hazard are found in: Osweiler et al. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Kendall/Hunt Publishing Company 1984; 374. - Available from amazon.com -

Treatment

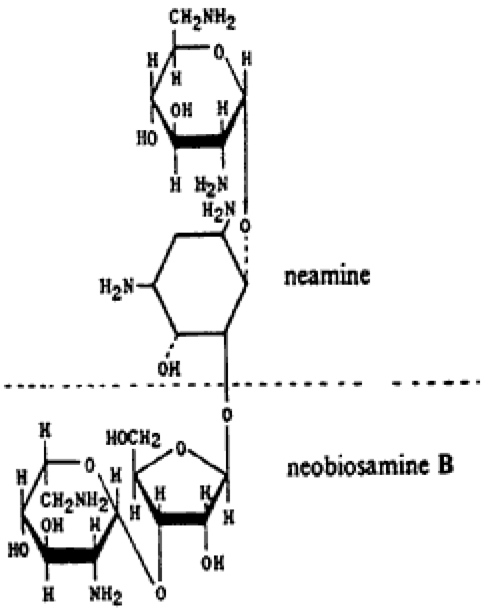
- Remove from source of gas. **Must consider human risks involved**. Provide good ventilation.
- Cardiopulmonary support and resuscitation. Hyperbaric oxygen therapy has been advocated in affected humans.
- Treatment for pulmonary edema if present.
- Nitrite administration and subsequent methemoglobinemia production (as per cyanide toxicosis) has been advocated for treatment. The goal is to result in sulfmethemoglobin which releases "nontoxic, oxidized forms of sulfur which are excreted primarily by the kidney". However, because of the inability of methemoglobin to carry oxygen, nitrite administration might contribute to the preexisting H_2S-induced cellular hypoxia. Efficacy of nitrite for H_2S toxicosis has not been critically examined or demonstrated in animals but it has been successful in the resuscitation of several human H_2S victims.

Aminoglycoside Antibiotics and Skeletal Muscle Relaxants

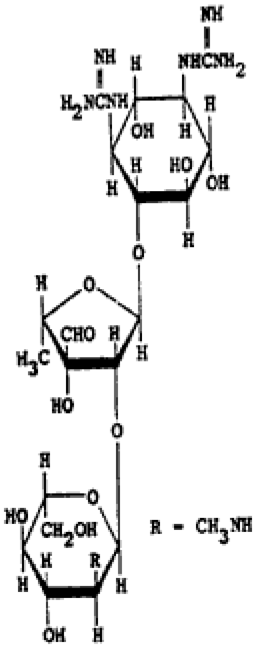
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Primarily Cause Respiratory Paralysis
All species	Minutes to hours	Hours to 2 days; may be lethal	

Sources

The aminoglycoside antibiotics kanamycin, tobramycin, gentamicin, neomycin, and streptomycin have all been shown to produce a neuromuscular blockade which may enhance the blockade of skeletal muscle relaxants. Other antibiotics which have been implicated in neuromuscular blockade include penicillin G and V, tetracycline, and polymyxin A and B.



Neomycin B



Streptomycin

Mechanism of Action

- Aminoglycoside antibiotics have several possible modes of action including postsynaptic receptor blockade, inhibition of acetylcholine release from nerve terminal, or local anesthetic-type of action.
- **Nerve terminal**-penicillin effect (which occurs only at massive doses) resembles anticholinesterase in action on the nerve terminal, producing prolonged negative after potential. May affect membrane sodium conductance.
- Polymyxins produce neuromuscular blockade (NMB) of complex and incompletely understood origin. Studies indicate postsynaptic site of action.
  Note - 4-aminopyridine can reverse NMB experimentally produced by polymyxins.
- The nephrotoxicity of gentamicin has been attributed to inhibition of phospholipases in lysosomes which results in a lysosomal storage disease.

Signs

- Onset between administration of last dose of antibiotic and onset of clinical symptoms has been reported from 1 - 26 hours.
- Human patients with myasthenia gravis appear at higher risk.
- The syndrome is well documented in man. Respiratory paralysis may occur from the use of aminoglycoside antibiotics alone or from the combination with surgical use of neuromuscular blocking agents.

- The antibiotic may cause such effects after administration by a variety of routes including: intramuscular, intravenous, subcutaneously, intraperitoneal, intrapleural, oral, and possibly others.
- Similar respiratory paralysis has been reported in a bird following an IM injection of gentamicin.
- Longer term exposure to aminoglycosides can cause renal failure.

Lesions

With renal failure, the epithelium of the proximal tubule (P3 segment) tends to be damaged.

Prevention

Prevention of the problem is the best approach. Aminoglycoside antibiotics should be administered only with extreme caution during surgery or in the postoperative period since the effect of surgical neuromuscular blocking agents may be enhanced.

Treatment

- Most life-threatening sign is hypoventilation.
  - Support of ventilation is essential.
- Treatment with calcium or anticholinesterase agents (neostigmine) has been associated with a degree of improvement in some cases.
- *In vitro*, the NMB and associated paralysis produced by streptomycin, kanamycin, and gentamycin is reversed (> 70%) by administration of calcium. Calcium has only slight effect on lincomycin and no effect on polymixin NMB.
- Calcium chloride or calcium gluconate may be administered IV. Calcium infusion should be performed slowly and with EKG monitoring for arrhythmias.
- Generally, neostigmine is less effective in reversing antibiotic-associated NMB.
- 4-aminopyridine has had some success *in vitro* in reversing antibiotic NMB.
  - **Note** - Gentamicin also can be directly cardiotoxic.

Section III: Toxicants that Cause Primary Muscle Dysfunction and/or Paralysis

Toxicants that Cause Primary Muscle Dysfunction and/or Paralysis

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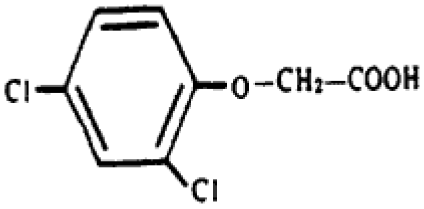
Phenoxy Herbicides

(2,4-D, MCPP, Silvex, 2,4,5-T, and Others)

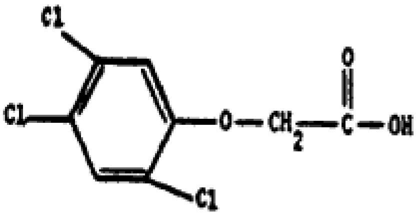
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Primary Muscle Dysfunction and/or Paralysis
Dogs, hervbivores	Within 24 hours	Days; rarely lethal	

Sources

- Phenoxyacetic acid (chlorinated) derivatives, such as 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), silvex, MCPP, MCPA, and others may possibly be involved.
- 2,4,5-T was contaminated with very toxic chlorinated dibenzodioxins, especially 2,3,7,8 tetrachlorodibenzodioxin, but these are not encountered in 2,4-D. Dibenzodioxins were the toxic contaminant found in the defoliant Agent Orange, which was a 50/50 combination of 2,4-D and 2,4,5-T.



2,4-dichlorophenoxyacetic acid (2,4,-D)



2,4,5-trichlorophenoxyacetic acid (2,4,5-T)

Toxicity

- In theory 2,4-D should not cause toxicoses in dogs which only have contact with it via lawns treated with the herbicide, when it is used at recommended rates. Whether there is a segment of the canine population that is exceedingly susceptible is unknown.
- 2,4-D.
  - LD_{50} dog 100 mg/kg (oral).
  - Lethal to dogs at 25 mg/kg/day for 6 days.
  - Oral LD_{50} rat 375 - 1,200 mg/kg.
  - Toxicity observed in calves at 200 mg/kg, swine 100 mg/kg.
- 2,4,5-T.
  - Oral LD_{50} dog approximately 100 mg/kg.
  - Oral LD_{50} rat 500 mg/kg, guinea pigs 381 mg/kg.
- MCPA.
  - Oral LD_{50} rat 612 - 1,200 mg/kg.
- Dicamba (a benzoic acid herbicide with some toxic effects similar to the phenoxy herbicides).
  - Oral LD_{50} 757 - 1414 mg/kg.

Mechanism of Action

2,4-D has a direct effect on muscle membranes causing increased irritability and rigidity followed by paralysis.

Susceptible Species

- Canids are predisposed as compared to other species possibly due to their poor ability to excrete organic acids in the urine.
- In practice, dogs do seem to eat inordinate amounts of phenoxy-herbicide treated grass.

Absorption, Distribution, Metabolism and Excretion (ADME)

- 2,4-D salts or esters are readily released in the gastric acid and rapidly absorbed due to protonation (addition of hydrogen ion) of the free anion in the gastric acid.
- Most of the herbicide is excreted in the urine as the unchanged acid.
- 2,4,5-T may undergo enterohepatic circulation.

Signs

- Dogs:
    - Often the only signs seen in the field from moderately toxic doses of phenoxy herbicides are related to gastrointestinal effects:
        - Vomiting.
        - Diarrhea, sometimes bloody.
    - With serious toxicosis as more often occurs after exposure to concentrates or pools of sprays, or when dogs are present and heavily exposed during spraying, muscular effects may predominate:
        - Hesitancy to move.
        - Rigidity of skeletal muscles.
        - Ataxia.
        - Weakness especially in the rear legs.
        - Clearly neurologic signs including seizures occur only with highly toxic doses.
        - Chronic spasms and coma. Opisthotonus occasionally occurs.
    - The most sensitive effect of 2,4-D toxicosis in the dog is found by use of the electromyogram. Greatly increased insertional activity (harmonic response upon insertion of the needle electrode) occurs at doses well below those causing notable clinical effects. This is an indication of a primary muscle effect of 2,4-D. At much higher doses, nerve degeneration which is at least partially reversible **may** also occur. This may be largely a result of damage to the nerve at the neuromuscular junction.
        - Additional effects, which may occasionally occur in dogs, include:
        - Oral ulcers.
        - Small intestine mucosal damage.
        - Renal tubular degeneration.
        - Focal hepatic necrosis.
- Ruminants:
    - Clinical signs include anorexia, depression, bloat, rumen atony, weakness, and diarrhea. Oral mucosal ulceration may be noted.
- Swine:
    - Display diarrhea, ataxia, depression, vomiting, and weakness.

Pathology

- Congestion of kidney, hyperemia of lymph nodes, and congested friable liver may be seen on postmortem examination.
- Rumen stasis commonly observed.
- Clinical pathological changes include elevation of CDK, SGOT, LDH.

Treatment

- Usually there is an oral exposure from drinking or eating the herbicide or from eating heavily treated grass. Grooming of 2,4-D from the body by the animal may prolong exposure.
- Therefore the use of activated charcoal and a saline cathartic for very recent exposures is indicated, along with a bath in a detergent.
- Ion-trapping of 2,4-D may enhance the removal from the tissues and promote its excretion in the urine. Fluids containing 1 - 2 mEq/kg bicarbonate are therefore indicated, if normal renal function is present.
- A bland diet and good nursing care should be provided.

Prognosis

Most animals should be expected to make an uneventful recovery.

Note

Phenoxyherbicides may cause an increased palatability of some types of poisonous plants due to abnormal plant carbohydrate metabolism. Phenoxy herbicides can also increase the concentration of nitrates and cyanogenic glycosides in some plants.

Additional Toxicants

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Primary Muscle Dysfunction and/or Paralysis
Monensin (Rumensin ®, Coban ®) (Ionophores*)	Horses, ruminants, poultry	Hours to days	Few days to permanent damage; cardiac involvement frequent in horses; often lethal	
Lasalocid (Bovatec ®) (Ionophores*)	Dogs, horses	Hours to days	Days to permanent damage; potentially lethal	
Salinomycin (Ionophores*)	Horses, cats	Hours to days	Days to permanent damage; potentially lethal	
Laidlomycin priopiopinate (Ionophores*)	Horses	Hours to days	Days to permanent damage; potentially lethal	
Narasin (Ionophores*)	Horses	Hours to days	Days to permanent damage; potentially lethal	
* **Ionophores**: (See Toxicants that Affect the Heart, Organic Compounds)				
Senna (*Cassia*) (See Toxicants that Affect the Heart)	Herbivores, poultry	Days to weeks	Weeks to permanent damage; potentially lethal	
Hairy vetch (*Vicia villosa*) (See Toxicants that Affect the Skin)	Herbivores, esp. black cattle	Days to months	Weeks to permanent damage; potentially lethal	
Lathyrus (vetchlings)	(See Toxicants that Cause Paralysis)			
Avocado (*Persea americana*) [See Galey F. In: Colgate SM and Dorling PR (eds.) Plant Associated Toxins: Agricultural, Phytochemical and Ecological Aspects. CABI	(See Toxicants with Mixed Effects on the Central Nervous System)			

Publishing 1997. - Available from amazon.com -]			
Thermopsis montana	Cattle	Weeks to months	Months to permanent damage; potentially lethal
Vitamin D-containg plants e.g. *Cestrum Diurnum* and *Solanum malacoxylon*	(See Nephrotoxic Plants)		

- Monensin (See Toxicants that Affect the Heart, Organic Compounds)
- Lasalocid (Bovatec) in dogs (See Toxicants that Affect the Heart, Organic Compounds)
- *Cassia* (See Toxicants that Affect the Heart)
- Lathyrus (See Toxicants that Cause Paralysis)
- Hairy Vetch (*Vicia villosa*) (See Toxicants that Affect the Skin)
- Thermopsis montana

Section IV: Toxicants that Cause Acidosis

Toxicants that Cause Acidosis

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Ethylene Glycol

(Conventional Radiator Antifreeze)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Acidosis
All species; esp. dogs, cats	30 min to a day	Days; often lethal	

Synonyms - Ethylene glycol, 1,2 ethanediol

Sources

- The primary ethylene glycol source that results in toxicosis is conventional automotive permanent antifreeze, which is approximately 95% ethylene glycol. Other heat exchange fluids, such as those used in solar collectors, ice rink freezing equipment, some brake and transmission fluids and diethylene glycol used in color film processing, may also serve as sources.

Structure

$HO\text{-}CH_2\text{-}CH_2\text{-}OH$

Susceptible Species

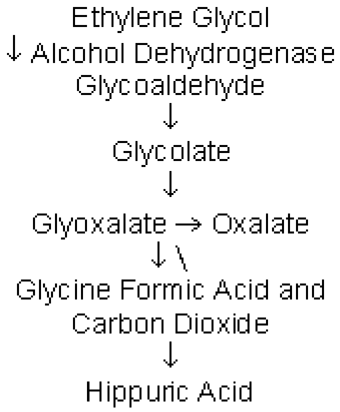
- Both birds and mammals are susceptible to ethylene glycol poisoning.
- Toxicosis is most common in young male dogs and cats. Cats are especially sensitive.
- Most poisonings occur between late fall and early spring. Animals consume ethylene glycol voluntarily, even when water is available.
- Due to delays in presentation and diagnosis and due to therapeutic limitations, a high death rate (78%) has been reported in dogs and cats. Poisoned animals are often presented without a history of exposure and are diagnosed postmortem or after damage has occurred.

Toxicity

Species	Lethal Dose Undiluted (95%)	Approximate Fatal Amount (50:50 - Antifreeze:Water)
Feline	As low as 1.5 ml/kg BW	A 5-kg cat would have to drink about 15 ml (1 tbsp) of diluted antifreeze
Canine	Minimum lethal dose of 6.6 ml/kg BW	Using a dose of 13.2 ml/kg diluted antifreeze, a 10-kg dog would have to drink about 132 ml or 4 1/2 oz of diluted antifreeze
Poultry	7 - 8 ml/kg BW	
Cattle	2 - 10 ml/kg BW (younger animals appear to be more susceptible)	

Absorption, Distribution, Metabolism and Excretion (ADME) and Pathogenesis

- Unmetabolized ethylene glycol has about the same toxicity as ethanol, and it is rapidly absorbed.
- Peak blood concentrations occur in dogs from less than 1 - 4 hours postexposure.
- At low doses, the plasma half-life of the parent compound ethylene glycol is 2.5 - 3.5 hours in the dog.
- Significant portions of ethylene glycol are excreted unchanged in the urine, especially during the first 4 hours, continuing for up to 24 hours.
- A knowledge of the metabolism of ethylene glycol is critical in understanding intoxication and making therapeutic choices.
- Metabolism occurs in the liver beginning with oxidation by alcohol dehydrogenase to glycoaldehyde. This step is the first of 2 important rate-limiting steps in the metabolism of ethylene glycol. Glycoaldehyde is more toxic than ethylene glycol, but it doesn't accumulate because it is readily metabolized to glycolic acid.
- The severe metabolic acidosis associated with ethylene glycol toxicosis in dogs is believed to result primarily from glycolic acid, which is more toxic than ethylene glycol. Urinary glycolate concentrations correlate with clinical signs, including mortality.
- The next step in metabolism, the conversion of glycolic acid to glyoxylic acid, is the other rate-limiting reaction. The slow degradation of glycolic acid allows time for it to cause acidosis and probably nephrosis. Glyoxylic acid is more toxic than any of the other metabolites, but its half-life is so short that the concentrations reached are probably too low to cause toxic effects. Glyoxylic acid can be converted to formic acid and carbon dioxide, and in some species the conversion to CO$_2$ is a major pathway. Glyoxylic acid may also be metabolized to glycine and serine, which enter the pool of amino acids via steps requiring pyridoxine as a cofactor. Some of the glycine reacts with benzoic acid to form hippuric acid. Glyoxylic acid may also be conjugated to produce oxalomalate, hydroxyketoglutarate and, using thiamine pyrophosphate, to hydroxy-ketoadipate.
- Another pathway of glyoxylic acid metabolism is oxidation to oxalic acid. It is estimated that between 0.25 - 3.7% of an ingested dose of ethylene glycol is converted to oxalate. Most oxalic acid is excreted in the urine, but some combines with calcium to form calcium oxalate crystals, a portion of which are precipitated in the renal tubules and to a lesser degree in the vasculature of the brain and other tissues. Nervous system effects of ethylene glycol toxicosis, however, do not correlate well with the presence of oxalate crystals, and in surviving animals complete recovery of the central nervous system (CNS) function is the rule.



Ethylene glycol metabolism. Different species favor different metabolic pathways.

Signs

- The diagnosis of ethylene glycol toxicosis is usually based on history of exposure, clinical signs, pronounced calcium oxalate and hippurate crystalluria, metabolic acidosis (blood pH less than 7.3) and azotemia with a dilute urine.
- When the clinical history is inadequate, crystalluria is absent or not yet developed, or the urinary bladder is empty, the poisoning is difficult to identify clinically.
- The clinical syndrome of ethylene glycol poisoning involves 3 main stages. The length of time between ingestion, onset of clinical signs, and progression through these stages is dose dependent and is influenced by the species involved. Stage 1 occurs within 30 minutes to several hours of ingestion, is characterized by central nervous system involvement, and mimics acute alcohol toxicosis.

- Intact ethylene glycol is a depressant and may cause drunkenness and ataxia approximately 1 hour after ingestion, but depression is often not noticed.
- Ethylene glycol induces diuresis: dehydration and polydipsia commonly result.
- After the initial depression and other direct effects of ethylene glycol, animals often recover and then rapidly deteriorate. This "recovery" may be due to dilution between ethylene glycol and glycolic acid: it is theorized that during this time neither compound may be present at a high enough concentration to cause pronounced signs.
- Dogs and cats may exhibit anorexia, ataxia may be pronounced in the hind limbs, depression, loss of reflexes, hypothermia, vomiting, coma, miosis, and death. Metabolic acidosis may be responsible in part for vomiting, tachypnea and weakness.
- Stage 2 occurs 12 - 24 hours postingestion and involves the cardiopulmonary system. Cardiopulmonary involvement includes tachypnea, tachycardia, or bradycardia. These clinical signs are infrequently observed in the dog and cat. Occasional acute (< 12 hours postingestion) deaths have been reported with ethylene glycol and may be due to cardiopulmonary failure.
- Stage 3 occurs 12 - 72 hours postingestion and is characterized by oliguric renal failure. This is the stage when animals are most commonly presented.
- Pain may be noted in the kidney area and dehydration is frequent. The kidneys may be enlarged on palpation.
- Numerous animals develop delayed depression, vomiting, polyuria and later oliguria or anuria, seizures, and oral ulcers-signs largely attributable to renal failure. Animals that survive longer may become cachexic.
- Ocular lesions potentially associated with ethylene glycol-induced renal failure include retinal detachment, retinal edema, and anterior uveitis.

Differential Diagnosis

- Primary confusion factors include other causes of acute CNS depression, acidosis and renal failure. Differential diagnoses to be ruled out include head trauma, encephalitis, acute nephritis and drug overdose. Poisoning may also be confused with acute diabetes mellitus.
- Cerebrospinal fluid parameters may suggest meningoencephalitis but are more often normal.
- No odor of alcohol is imparted to animals by ethylene glycol.

Clinical Pathology

- Mild mature lymphopenia and mild mature neutrophilia (stress leukogram) may occur. Hemoconcentration as reflected by increased packed cell volume (PCV) and total protein often occurs in clinically dehydrated animals.
- As the syndrome progresses, increases in blood urea nitrogen (BUN), creatinine and phosphorus are quite common, and in most dogs and cats hyperglycemia and hypocalcemia may occur. Hypocalcemia may contribute to hyperglycemia by inhibiting insulin secretion. Hyperglycemia may also be due to the effects of aldehydes on inhibition of glycolysis and the Krebs cycle due to the severe depletion of NAD^+ brought about by the metabolism of ethylene glycol.
- Hyperkalemia attributable to renal failure and/or acidosis may also be present.
- Hypochloremia and low blood bicarbonate concentrations often develop.
- The overall blood gas picture reflects a metabolic acidosis. Hypocalcemia occurs in many acidotic states due to competitive displacement of calcium from serum albumin by hydrogen ions. The displaced calcium diffuses into the cells or is eliminated, lowering the total blood calcium. This apparently occurs in ethylene glycol toxicosis. Oxalic acid may also lower blood calcium due to precipitation of calcium oxalate in tissues and excretion in the urine. Serum calcium declines while urinary calcium greatly increases. It is uncertain whether the hypocalcemia in ethylene glycol toxicosis is responsible for CNS or cardiac malfunction since the ionized (active) calcium of the blood is maintained even as the albumin-bound calcium declines.
- Increased anion gap and osmolal gap are often present and are used as diagnostic aids in ethylene glycol toxicosis. The combination of a severe, high anion-gap metabolic acidosis with a high osmolal gap also occurs in methanol toxicoses; but only with ethylene glycol are oxalate and hippurate crystalluria prominent.
- The anion gap is computed as the serum sodium plus potassium minus the sum of serum chloride and bicarbonate ($[Na^+] + [K^+] - \{[Cl^-] + [HCO_3^-]\}$). The normal anion gap is about 10 - 15 mEq/L. A value of greater than 25 mEq/L is assumed to represent an excess accumulation of unmeasured anions (ethylene glycol metabolites). It may be noted that ketoacidosis, renal failure, lactic acidosis,

administration of amino acids with sorbitol, and salicylate and paraldehyde toxicoses may also cause a high anion gap.

- Osmolality is a measure of the number of molecules in a solution. The osmolal gap is the difference between the measured and calculated serum osmolality. The molecules which contribute most to serum osmolality are sodium, chloride, bicarbonate, glucose and urea. Most laboratories express electrolytes as mEq/L (same as mmol/L for monovalent anions) and the usual units for glucose and urea are mg/dl. Dividing glucose by 18 and BUN by 2.8 as shown in the formula below equilibrates the laboratory values to equivalent mmol/L values:

$$\text{Calculated Serum Osmolality in mOsm/L} = 1.86\,(\text{Na} + \text{K in mEq/L}) + \frac{\text{Glucose in mg/dl}}{18} + \frac{\text{BUN in mg/dl}}{2.8} + 8.6$$

The constant 8.6 is added as an estimate of normal, osmotically active solutes, e.g., calcium, phosphate, and creatinine.

- Plasma osmolality may also be measured directly using freezing point depression (1.86 ºC for every osmol of solute). In the normal animal the calculated serum osmolality is within 5 - 10 mOsm/L of the measured osmolality. When measured osmolality is more than 10 mOsm/L greater than the calculated osmolality, an osmolal gap is said to exist. If the measured osmolality is not lowered by the presence of water-insoluble molecules such as lipids, the gap represents large numbers of other molecules, such as ethylene glycol and its metabolites. Ethylene glycol increases the measured osmolality by depressing the melting point of the plasma. Since its presence is not accounted for in the formula above, it also increases the osmolal gap. Normal osmolality for dogs and cats is 280 - 310 mOsm/L, and measured values in early ethylene glycol toxicosis may be increased by as much as 60 mOsm/L.
  Note - In the later stages of ethylene glycol toxicosis, no osmolal gap may be present. Other causes of an increased osmolal gap include ethanol, methanol, isopropanol, acetone, mannitol, sorbitol and diatrizoate (IVP dye). Ethyl ether and trichloroethane may cause an increase in osmolal gap but not metabolic acidosis. Isopropanol toxicosis may also cause ketosis and depression of the CNS but not metabolic acidosis.
- Most urine specific gravities are in the isothenuric range (1.008 - 1.012); and the others are frequently dilute (1.013 - 1.025) in spite of dehydration. Acid urine, hematuria, proteinuria and glucosuria are frequently observed. Cats often develop coffee-colored urine.
- Urine sediments often contain red and white blood cells, renal epithelial cells, casts and calcium oxalate and especially hippuric acid crystals. Both types of crystals are similar in shape, and both are highly birefringent. To identify birefringence, two polarized lenses (as in a pair of polarized sunglasses) are laid over one another either above or below the stage of the microscope and one is rotated so as to darken the field of view. Crystals which stand out as strikingly bright against the dark background are birefringent. The same technique is used to examine kidney biopsies, impression smears and histologic sections (see Diagnosis).

Gross Lesions

- Some dogs have severe dehydration.
- Hyperemia of the gastrointestinal tract, swollen kidneys, and pulmonary edema may occur.
- If the animal lives long enough to become uremic, there may be significant weight loss, oral ulcers and hemorrhagic gastritis.

Microscopic Lesions

- Calcium oxalate or hippurate crystals can usually be seen in renal impression smears and especially histologic sections. Blood vessels of the brain and muscle may occasionally have crystals present as well.
- In ethylene glycol nephrosis, renal tubules are usually very dilated, but the tubular pathology is not always accompanied by oxalate crystals.
- There is generally little reaction to the crystals, and healing occurs despite their presence. In surviving animals, the renal lesions generally resolve, but in a few cases chronic fibrosing renal damage occurs.

Diagnosis

- Diagnosis of ethylene glycol toxicosis often requires a known or suspected exposure history, appropriate clinical signs (most commonly ataxia, depression, vomiting, hypothermia, anuria, or oliguria), alterations in the serum chemical profile (azotemia, hyperphosphatemia, hypocalcemia, and hyperglycemia), and urinalysis (isothenuria, calcium oxalate, and possibly hippurate crystalluria). The oxalate crystals may take the appearance in urine of 6-sided prisms, dumbbell, "hempseeds", or 6-sided prism with 4-sided crystals budding from their surfaces.
- Analysis for ethylene glycol in blood or urine is a specific test but, due to metabolism, is practical only in the early stages (first 12 - 24 hours) of toxicosis. In ethanol-treated animals, inhibition of metabolism of the parent compound may prolong the presence of ethylene glycol in blood and urine.
- Colorimetric kits are on the market for in-house analysis. Their sensitivity should allow them to be useful if the poisoning has occurred within 24 hours.
- Analysis of serum for glycolic acid may be preferable since detection is possible from 3 - 60 hours after ethylene glycol ingestion.
- High hippurate concentrations also occur in the urine of ethylene glycol-poisoned dogs.
- Unfortunately, ethylene glycol, glycolic acid and hippurate analyses are not rapidly available to most practitioners.
- Ethylene glycol is not identified in some coma screens which may include some other alcohols, barbiturates, nonbarbiturate hypnotics, tranquilizers, salicylates and carbon monoxide.
- These obstacles and the availability of electrolyte, blood gas and serum chemistry assays in clinical pathology laboratories make it such that serum anion and osmolal gaps may be more immediately useful in diagnosis.
- Kidney calcium concentrations tend to be very high-often between 1,000 and 10,000 parts per million as compared to control values in the range of 100 parts per million.

Prognosis

- Dogs with very low blood pH, severe base deficit and high venous PO_2 (associated with increased respiratory rate and decreased activity) are less likely to respond to treatment.
- At 30 hours after exposure, persistence of hypothermia, hypocalcemia and elevations of phosphorus, BUN and creatinine all indicate a poorer prognosis.
- Some dogs presented in a coma after ethylene glycol ingestion should be given a poor prognosis since they are frequently in a terminal state of either acute intoxication or renal failure with uremia.

Treatment

- Animals allowed to eat and drink during all courses of therapy.
- A few hours delay before specific treatment is instituted can make a grave difference.
- In very early cases, when coordination and postural and gag reflexes are intact, emetics should be given.
- Despite some suggestions that it may not bind ethylene glycol, activated charcoal (1 - 2 grams/kg) and a saline cathartic (250 mg/kg), such as a magnesium or sodium sulfate solution, may be given by stomach tube when animals are presented within the first 3 hours of ingestion. If an emetic is used, the charcoal and saline cathartic are given after vomiting has subsided.
- The use of ethanol and bicarbonate with fluid therapy is widely accepted. Ethanol competitively inhibits alcohol dehydrogenase, allowing more unmetabolized ethylene glycol to exit via the urine. The development of acidosis is thereby reduced.
- Sodium bicarbonate is used to correct the metabolic acidosis and to ion-trap metabolites, thereby reducing their diffusion into the cells and enhancing their removal in the urine.
- **Note** - *Treatment with ethanol or 4-methylpyrazole is not indicated in patients that are already in oliguric renal failure*. In these patients, fluid, electrolyte, and acid-base abnormalities should be corrected.
- Treatment results are not ideal. Problems with ethanol-bicarbonate therapy include:
    - Animals that may already be depressed are given another CNS depressant.
    - To allow for ethylene glycol excretion, it is necessary to maintain a blood level of ethanol for up to 72 hours.
    - In dogs, ethanol may fail to prevent death when ethylene glycol at 10 ml/kg is ingested and treatment is started as early as 1 hour thereafter.
    - When animals are first presented 18 or more hours after exposure, fluid therapy with sodium bicarbonate is strongly indicated but ethanol, if started at this point in time, would usually do more harm than good, since it is assumed that almost all the ethylene glycol would be past the

  first metabolic step. This assumption needs to be tested with dogs given high doses of ethylene glycol to determine if zero order (saturated) kinetics for alcohol dehydrogenase may be applicable. If this is the case, it may be appropriate to use alcohol dehydrogenase inhibitors at later times.
  - Ethanol enhances the diuresis initiated by ethylene glycol.
  - Pulmonary edema is more often a complicating factor in ethanol-treated animals.
- One treatment approach **for dogs** includes 20% ethanol in saline intravenously (IV) at 5.5 ml/kg and 5% bicarbonate intraperitoneally (IP) at 8 ml/kg. Both agents are administered initially, then every 4 hours for five treatments and finally every 6 hours for a minimum of four more treatments. Between doses, animals can be re-evaluated, and those regaining consciousness are given more favorable prognosis.
- **In cats**, a recommended dose for ethanol has been 5 ml/kg of a 20% solution and for bicarbonate 6 ml/kg of a 5% solution. Both are given IP every 6 hours for 5 treatments, then every 8 hours for 4 more treatments.
- The ethanol therapy is prolonged in all species. This is necessary since, although the production of toxic metabolites is reduced and more unchanged ethylene glycol is excreted in the urine, the overall result is nevertheless a great increase in the half-life of ethylene glycol in the blood.
- The experimental use of **low-dose** ethanol**-**sodium bicarbonate when given 1 hour after ethylene glycol administration prevented the development of ethylene glycol toxicosis. A solution of 30% ethanol, 1% sodium bicarbonate in 0.9% saline is given by rapid infusion at 1.3 mL/kg; the infusion rate is then reduced to 0.42 ml/kg/hour. The goal is to maintain blood ethanol at 50 mg/dl for 48 hours. The effectiveness of low-dose ethanol therapy when started beyond 1 hour postingestion has not been adequately characterized at this time.
- Bicarbonate may be used judiciously in the fluids in an attempt to maintain the urine pH at or above 7.0 - 7.5.
- **The dosages and routes of administration of sodium bicarbonate recommended above are somewhat controversial**. Sodium bicarbonate therapy preferably should be based on serial plasma bicarbonate determinations using the following formula:

  Bicarbonate Deficit (in mEq) =
  0.5 x Body Weight (in kg) x [24 - Plasma Bicarbonate (in mEq/L)]

  Note - In order to prevent overdose, only 80% of the calculated dose (in mEq) is given, and this must be done very slowly in the fluids if given by the intravenous route (i.e., give over 4 - 6 hours).

- Plasma bicarbonate should be checked every 4 - 6 hours. When actual plasma bicarbonate measurements cannot be performed and the clinical history and signs are highly supportive of acidosis due to ethylene glycol toxicosis, a plasma bicarbonate value of 8.5 mEq/L value may be assumed for significantly affected animals, and using the 80% safety factor one can calculate an estimated dose of sodium bicarbonate of 6.2 mEq/kg bw, which is equivalent to 10.4 ml/kg bw of a 5% solution of sodium bicarbonate, every 4 - 6 hours given slowly IV in fluids.
- **Correction of the acidosis** does not decrease the depth of coma, but **it greatly increases the chances for survival**.
- **Fluids are essential** to correct dehydration, increase tissue perfusion, alleviate acidosis, promote excretion of ethylene glycol and its toxic metabolites and avoid concentration of these nephrotoxic compounds in the kidneys. Fluid volumes depend upon the deficit, maintenance needs and continuing losses of the patient.
- Monitoring urine output, body weight, and central venous pressure is helpful in assessment of renal function and avoiding overhydration, which may cause or aggravate pulmonary edema, especially in anuric animals.
- The renal clearance of ethylene glycol varies inversely with tubular water reabsorption; therefore, after hydration is reestablished and, provided there is no evidence of pulmonary edema in the patient, osmotic diuretics such as 50% dextrose or mannitol may be used to promote excretion and reduce intrarenal edema.
- When oliguria or anuria are not correctable or when life-threatening toxicosis exists, peritoneal dialysis may be used. Dialysis is intended to remove ethylene glycol and its toxic metabolites and to alleviate uremia and acidosis.
- Peritoneal dialysis can be performed with a column-disk peritoneal catheter placed into the ventral abdominal cavity. Peritoneal dialysis involves instilling 1.5% dextrose (37 ºC) with 125 mg of cephradine/l and 500 U heparin/l added to alternate exchanges. Dialysate is instilled at a rate of 5 - 20 ml/kg by gravity. Dialysate is allowed to remain in the peritoneal cavity for 1 - 2 hours. Dialysate is then

drained from the peritoneal cavity. Peritoneal dialysis can be associated with mild peritoneal irritation and hypothermia if inadequately warmed dialysate fluids are used.

- Hemodialysis is very effectively used to remove ethylene glycol in humans and may be used with concomitant ethanol therapy. A high bicarbonate dialysate is much safer than standard acetate dialysates, which may further deplete the patient's serum bicarbonate.
- Pyridoxine and thiamine are suggested since they are cofactors in the metabolism of glyoxylic acid in pathways that do not lead to oxalic acid.
- Calcium may be given judiciously if hypocalcemia occurs (especially if the animal has low **ionized** calcium).
- Pyrazoles, butanediol and propylene glycol are alcohol dehydrogenase blockers that have been used to treat dogs, monkeys, and rodents in experimental ethylene glycol poisoning. Treatment with **4-methylpyrazole** has been recently advocated for ethylene glycol toxicosis in dogs. The recommended dose **for the dog** is an initial IV dose of 20 mg/kg using a 5% solution, then 15 mg/kg IV at 12 and 24 hours and 5 mg/kg IV at 36 hours after the first dose. The use of 4-methylpyrazole is not associated with the severe CNS depression as occurs in high dose ethanol therapy. To use 4-methylpyrazole, it is important to work with a compounding pharmacist and to have this individual prepare a sterile dosing solution. Aldrich Chemical of Milwaukee, WI, and Sigma Chemical Company of St. Louis, MO, sell the 4-methylpyrazole. It apparently is no longer necessary to receive FDA approval for this use of 4-methylpyrazole. The solution is made up by combining 5 grams of 4-methylpyrazole with 45 ml of polyethylene glycol 400. Then, with continuous stirring, 50 ml of bacteriostatic water is slowly added. The solution is then filtered with a 0.22 micron filter. The refrigerated solution is stable for at least one year. At the current time no safe and effective dosages of 4-methylpyrazole have been identified for domestic cats. Ethanol remains the alcohol dehydrogenase inhibitor or choice for cats. It presently appears that 4-methylpyrazole has some advantages over ethanol in the dog while the reverse is clearly true in the cat.
- The use of vasopressor agents (e.g., dopamine 2 - 3 µg/kg/minute IV) and diuretics (e.g., furosemide 2.2 mg/kg, q8h, IV) may be required to correct unresponsive anuria and/or pulmonary edema.

Propylene Glycol Antifreeze

- Less toxic than ethylene glycol but still somewhat toxic.
    - Oral LD_{50} dog - 19 - 22 ml/kg.
    - Rapidly absorbed with peak blood levels at 1 hour after ingestion.
- Metabolized by alcohol dehydrogenase to lactaldehyde which is converted to lactic acid but most leaves the body as parent compound or as a glucuronide conjugate (with the possible exception of cats).
- Treatment.
    - Limit absorption.
    - Fluids.
    - Bicarbonate as needed for acidosis (slow in the fluids).
    - Assist respiration if needed.

Methanol

(Methyl Alcohol, Wood Alcohol)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Acidosis
Mostly pet animals	Minutes to hours	Few hours to 2 days; potentially lethal	

Sources

Methanol is encountered most commonly in windshield washer antifreeze/cleaner solutions for automobiles. In years past, it was used as antifreeze for automobile radiators and is still used in air brakes and as an antifreeze for gasoline and diesel fuel. It is sometimes used as a fuel for some picnic stoves, in soldering torches, and in denaturing ethanol, although not all denatured ethanol contains methanol.

Structure

CH_3-OH.

Toxicity

- Toxicosis may result from oral, inhalation, or percutaneous exposure.
- Minimal lethal dose:

Rat	9.5 g/kg
Rabbit	7.0 g/kg
Dog	8.0 g/kg
Rhesus monkey	3 g/kg

- Approximate lethal dose in man: 1 g/kg.
- The toxicity of methanol, at least in humans, is, however, quite variable. Deaths have been reported following ingestion of 15 ml of 40% methanol, yet survival has been documented after ingestion of 500 ml of the same concentration. The usual fatal dose of absolute methanol in humans is 100 - 250 ml.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rapidly absorbed from the stomach.
- The half-life of methanol elimination in the dog has been reported to be 43 hours.
- Oxidation by hepatic metabolism to formaldehyde and formic acid.
- Initial reaction is often catalyzed by liver alcohol dehydrogenase. In some species, oxidation of methanol and formate is by the catalase-peroxide enzyme system.
- Formic acid and formaldehyde excreted in the urine.
- Formic acid inhibits cytochrome C oxidase, succinate-cytochrome C reductase, and catalase enzyme activity.

Signs

- Methanol causes three primary effects: **1**) CNS, **2**) metabolic acidosis, and **3**) in man, rhesus monkeys, and possibly some non-primate animals, ocular signs occur. Ocular problems do not seem to be a problem in dogs.
- Signs may appear from 40 minutes (CNS signs) to 72 hours (ocular effects) after exposure (at least in man).
- CNS.
    - Depression, malaise, ataxia, weakness, and coma. Convulsions are sometimes reported. Ataxia, depression, and hyperexcitability were observed in experimentally poisoned dogs; signs developed from 15 minutes to 5 hours post-exposure.
- Metabolic Acidosis:
    - An anion-gap, metabolic acidosis is a classical finding in human methanol toxicosis. If plasma osmolarity is measured using a freezing point determination, methanol, like ethanol and ethylene glycol, will cause an osmolal gap.
    - Methanol is associated with abdominal pain and like other conditions in which a metabolic acidosis occurs, vomiting commonly occurs, although the absence of vomiting or abdominal pain does not rule out methanol toxicosis.
    - Metabolic acidosis was reproduced in only 10 - 15% of experimentally exposed dogs. Metabolic acidosis can be reproduced in experimentally poisoned rhesus monkeys.
    - Formic acid is thought to contribute to the development of a metabolic acidosis.
    - If metabolic acidosis occurs, tachypnea should be expected as the animal attempts respiratory compensation.
- Ocular:
    - Ocular lesions in experimentally poisoned rhesus monkeys include optic disc edema, identical to that caused by increased intracranial pressure. Retinal vessels appear engorged.

    - Formate is considered to be the most important toxic metabolite. Administration of formate or formic acid will reproduce clinical signs and ocular manifestations in rhesus monkeys.
    - Formaldehyde is rarely detected in vitreous and aqueous humors. By contrast, administration of formaldehyde will not reproduce clinical signs of blindness, however changes in electroretinograms (ERG) occur.
    - As little as 4 ml of absolute methanol has caused blindness in humans.
    - Humans:
        - Fundiscopic examination may be normal, or there may be papillary or retinal edema, and/or hyperemia of the optic disc. Later retinal atrophy may occur.
        - Early blurred vision often occurs and frequently the syndrome terminates in blindness.
- Respiratory:
    - Respiratory arrest occasionally occurs in experimentally poisoned dogs and monkeys.
    - Death may result from sudden respiratory failure in the terminal stages of poisoning. In humans, opisthotonus is followed by a deep gasp and locking of the chest in the full inspiratory position, while the heart temporarily continues beating.

Diagnosis

- History of ingestion.
- Anion-gap, metabolic acidosis; possible osmolal gap.
- Plasma bicarbonate may sometimes be severely decreased.
- Urine pH also low.
- Pancreatic necrosis has been reported, and pancreatic enzymes may be elevated.
- Blood methanol concentrations may be determined at certain human hospitals or other toxicology laboratories.
- Detection of formaldehyde in urine, blood, and other tissues.

Treatment

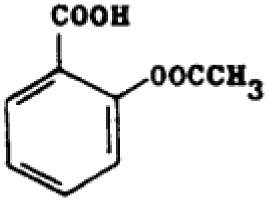
- Check and maintain respiration.
- Methanol is rapidly absorbed from the stomach. Therefore, emesis should be instituted only if presented very shortly after ingestion (less than 1 hour?) and only if the animal is alert and has intact postural and gag reflexes.
- Activated charcoal (1 g/kg) would have limited value due to low affinity for methanol.
- Saline cathartic (sodium or magnesium sulfate: 250 mg/kg as a 10 - 20% solution in water; may be mixed with activated charcoal).
- At the present time, treatments for poisoned animals generally include therapy to reduce metabolic acidosis and, in the case of primates, to slow the production of formate and formaldehyde. The effectiveness or necessity of these therapies in nonprimate animals is not proven. The need is likely to vary among animals with some experiencing significant benefit.
- Administer fluids with sodium bicarbonate (as needed) at up to 1 - 2 mEq/kg every 1 - 2 hours (slowly in the fluids); blood gases may be used to determine bicarbonate deficit to adjust therapy (see Ethylene glycol section).
- For primates, ethanol is recommended as an inhibitor of alcohol dehydrogenase as per ethylene glycol intoxication. Methanol has roughly 20 times less affinity for alcohol dehydrogenase than ethanol and is metabolized at 1/5 the rate of ethanol. Therefore, ethanol must be administered periodically. Although not adequately studied at this time, it seems likely that 4-methylpyrazole could be used instead of ethanol (see section on Treatment under Ethylene Glycol).
- Monitor glucose and potassium; hypokalemia in the presence of acidosis is a bad prognostic sign.
- Leucovorin (folinic acid) and folic acid decrease the persistence of formic acid and promote its conversion to carbon dioxide and water.

Aspirin and Salicylates

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Acidosis
Cats, dogs	Minutes to chronic	Days; potentially lethal	

Sources

- Aspirin (acetylsalicylic acid; alternative name is 2-acetyloxy-benzoic acid) is a phenol derivative and is often available in 5 or 7.5 grain (325 - 500 mg) tablets.
- Salicylates in common use also include sodium salicylate and salicylic acid.
- Products containing aspirin also include: Alka-Seltzer, Aspergum, Bufferin, APC, Anacin, etc.
- Salicylates are commonly combined with other drugs including caffeine, codeine, and acetaminophen.
- Pepto Bismol liquid contains bismuth subsalicylate at a concentration of 262 mg/15 ml which equals 130 mg of salicylate/ml.
- Salicylates are also contained in topical preparations (e.g., methyl salicylate [oil of wintergreen]) are used as keratolytic agents.



Aspirin (acetyl-salicyclic acid)

Toxicity

- An aspirin dosage of 25 mg/kg once daily will produce a serum salicylate concentration in the cat which is equivalent to that providing a therapeutic effect in man.
- Cats given one 5-grain tablet of aspirin per day (80 - 120 mg/kg/day) developed clinical signs of poisoning within 12 days.
- Administration of aspirin to dogs at a rate of 25 - 35 mg/kg every 8 hours provided an "optimal" serum salicylate concentration.
- Dogs given 100 - 300 mg/kg/day developed gastric ulceration and hematemesis within 1 - 4 weeks. At a lower dose of 50 mg/kg/12 hours, vomiting was seen approximately 2 hours after each dose.

Mechanisms of Action

- Aspirin blocks the activity of cyclooxygenase, an important enzyme in the pathway leading to prostaglandin synthesis. The net result is a decrease in concentration of prostaglandins.
- Similarly, by inhibition of platelet cyclooxygenase, there is an increase in bleeding time due to the decreased aggregation of platelets.
- At high doses, aspirin and other salicylates may uncouple oxidative phosphorylation and may cause hyperglycemia and glycosuria. Occasionally hypoglycemia is seen.
- An early effect may include stimulation of the respiratory center, which may result in respiratory alkalosis and secondary bicarbonate excretion in the urine. This stage will probably never result in presentation to the veterinarian, although persons aware of the significance of overexposure may bring animals in during this phase.
- A metabolic acidosis results from several aspects of the toxicosis:
    - Salicylates are weak acids; however, due to their high degree of protein binding and low plasma concentrations, it is unlikely that this is the cause of the acidosis.
    - An anion gap is produced in part by the presence of salicylic acid and other salicylate metabolites. Lactic acidemia develops secondarily from inhibition of normal glycolysis and contributes to the development of metabolic acidosis.
    - The early respiratory alkalosis may stimulate renal excretion of bicarbonate.
    - Metabolic derangement and resultant production of acetoacetic acid and other ketone acids have been reported.
    - Decreased renal excretion of sulfate, phosphate, and other acidic moieties may occur.

Absorption, Distribution, Metabolism and Excretion (ADME)

- The acid pH of the stomach protonates the acetylsalicylic acid, and as a result, the uncharged form is readily absorbed directly through the gastric mucosa. Significant absorption, however, also occurs in the small intestine.
- Enteric-coated aspirin formulations may delay and prolong absorption. In dogs dissolution and absorption of aspirin from enteric coated products was extremely variable.
- Plasma esterases rapidly hydrolyze aspirin to free salicylic acid.
- Aspirin is eliminated principally as free salicylic acid and as a conjugate of either glycine or glucuronic acid. Because of the limited capacity of cats to conjugate some xenobiotics including aspirin via the glucuronidation pathway (limited glucuronyl transferase), cats and neonates of many species are predisposed to toxicoses.
- Salicylates are extensively bound to plasma albumin.
- Serum half-lives in the cat were dose dependent:
    - 5 mg/kg BID - 21.8 hours.
    - 12 mg/kg/day - 26.8 hours.
    - 25 mg/kg/day - 44.6 hours.
- Half-lives for elimination include cat - 37.6 hr, dog - 8.6 hr, swine - 5.9 hr, horse - 1.0 hr, goats - 0.8 hr, and cattle 0.5 hr.

Signs

- Respiratory stimulation, tachypnea, and hyperventilation.
- Acidosis may require 12 - 24 hours to develop based on human literature.
- Fever with extremely high doses.
- Gastric irritation is the most common adverse side effect of aspirin.
- Gastric ulcers, with hematemesis in dogs or cats.
- Vomiting. In humans, vomiting commonly occurs 3 - 8 hours postingestion. May be blood tinged in 10 - 20% of toxicosis cases. Dogs may vomit within 2 hours of exposure.
- Anorexia.
- Dehydration, occasionally anuria develops.
- Depression. Animals may develop semi-comatose states. Muscular weakness.
- Toxic hepatitis (sometimes).
- Anemia, with Heinz bodies and reduced RBC production in cats.
- Pulmonary edema may occur.
- Ototoxicity reported in man due to increased labyrinth pressure.
- Convulsions and cerebral edema occasionally occur in animals. Seizures may be related to the effects of hyperventilation and/or reduced cerebral glucose concentrations.
- Death.

Clinical Pathology

- Hyperglycemia or hypoglycemia can occur.
- Hypokalemia and hypernatremia can occur.
- Large doses in humans have been associated with interference with the production of vitamin K dependent clotting factors, with secondary hypoprothrombinemia and hemorrhage.
- In the cat, Heinz body production and possibly hemolysis and bone marrow suppression may result in anemia.

Diagnosis

- Blood or serum salicylate concentrations are used routinely in human medicine, but concentrations associated with toxic effects have not been defined in veterinary medicine. Extrapolation from man could nevertheless be attempted.
- Toxic concentrations in human blood are reported to be 50 - 100 mg/dl, while concentrations of less than 50 mg/dl rarely produce serious toxicosis. In cats, 60 mg/dl has been associated with deaths.
- History of excessive exposure and appropriate acid-base alterations and clinical effects are important in establishing a diagnosis.

Treatment

- For very recent exposure and provided no contraindications exist, an emetic may be used.
- Activated charcoal and a saline cathartic may be used.
- Gastric lavage may be required. Effectiveness of activated charcoal and/or lavage may be prolonged (6 - 12 hours postingestion) if enteric-coated formulations have been ingested. Occasionally aspirin tablets may form insoluble concretions causing slowed but very prolonged absorption.
- Metabolic acidosis is treated by very slow infusion of sodium bicarbonate (1 - 3 mEq/kg) in fluids IV. This may also enhance the removal of acetylsalicylic acid and other acidic metabolites in the urine to shorten the duration of the whole syndrome. Bicarbonate and fluid therapy must be monitored closely and be adjusted if pulmonary edema develops. Development of diuresis may be delayed 1 - 4 hours (or more) and circulatory overload can develop. Diuresis may be promoted with the loop diuretic furosemide. The use of mannitol is generally not recommended.
- Intravenous glucose may be needed if the animal is hypoglycemic.
- If indicated, correction of electrolyte imbalance may be of value.
- Whole blood transfusions may be used if significant hemorrhage or anemia has occurred.
- Hyperthermia or hypothermia is controlled by external manipulation, not by drugs.
- In severe overdose, salicylates and metabolites may be removable by osmotic (alkaline) peritoneal dialysis as well as by hemodialysis.
- Exchange transfusions are sometimes used in pediatric human patients and could be employed in small animals as well.
- Misoprostol, a prostaglandin E_1 derivative, may help prevent aspirin-induced gastric ulcers.
- Sucralfate (synthetic dissacharide; Carafate ®) probably should be given if gastric erosions have occurred.

Other Agents that Cause Acidosis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Acidosis
d,l-Methionine	(See Toxicants with Mixed Effects on the Central Nervous System)			
Phenolics	(See Hepatotoxic Drugs and Chemicals)			
Any shock-inducing syndrome (metabolic acidosis)	-	-	-	
Any syndrome with prolonged exertion or seizures (metabolic acidosis)	-	-	-	
Any Syndrome with severe pulmonary failure or respiratory paralysis (respiratory acidosis)	-	-	-	
Other agents that cause acidosis	-	-	-	

- Any toxicoses which cause profound circulatory shock may cause a secondary metabolic acidosis.
- Toxicoses that cause prolonged seizures may cause acidosis due to the extreme exertion and exhaustion involved.
- Uncouplers of oxidative phosphorylation may cause significant acidosis.
- Phenolics may cause respiratory alkalosis caused by stimulation of the respiratory center which may later be followed by a metabolic acidosis. Phenolics will be discussed under toxicants that affect the liver. In general the phenolics exert effects on the gastrointestinal tract, the liver, the kidneys and sometimes the nervous system (infrequently seizures have been associated with phenol toxicoses).

Section V: Toxicants that Cause Fevers

Toxicants that Cause Fevers

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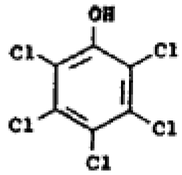
Pentachlorophenol

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Fevers
Most species	Hours	Days for most compounds; often lethal	

Sources

- Also referred to as penta and "PCP" although the latter term should be avoided due to its street use as a term denoting phencyclidine, which is also known as Sermylan®, or "angel dust".
- Pentachlorophenol was, until recently, the most commonly employed chemical in wood preservation. It was principally applied in hydrocarbon solvents as pentachlorophenol itself, although some sodium pentachlorophenate, which is water solubilized has also been used. Pressure-treated often meant "penta-treated", but at the present time, pressure-treated usually means treated with CCA (copper chromated arsenic).
- Pentachlorophenol is still sometimes used in light oils for brush-on application to wood, often used on natural, outdoor wood surfaces. Should never be applied indoors.
- "Penta"-treated feed and water troughs, fencing, and barn boards have been sources of contamination of livestock.
- Pentachlorophenol pressure-treated wood would sometimes "bleed" when it was relatively new. Its application under pressure would heavily soak the wood. Generally 11 g of penta was applied per board foot.
- Light solvent-based products may sometimes crystalize on wood surfaces and become airborn or sublime into sufficiently warm, enclosed surroundings.
- Miscellaneous other applications involve the herbicidal, fungicidal, insecticidal, bacteriocidal and molluscacidal (biocidal) properties of pentachlorophenol.
- Has been used in treatment of leather and in paper (to control mildew), in rug shampoos and for mothproofing of fabrics.
- Most wood is at least surface treated with a wood preservative to prevent mildew during shipping.
- Many other commonly used wood preservatives are also highly toxic. They may contain creosote (a phenolic), and the previously mentioned copper chromated arsenic (which causes effects most like arsenic toxicosis), among other possibilities. Such toxicants have a different spectrum of effects than those of pentachlorophenol.
- Homes constructed from pressure-treated (penta) wood had to be abandoned due to apparent toxicosis in their human occupants.
- Pentachlorophenol residues may also occur in animals as the result of the breakdown of hexachlorobenzene (HCB) or pentachlorobenzene. Up to 38% of an ingested HCB dose can be excreted as PCP.



Pentachlorophenol

Toxicity

- In all species evaluated, including domestic animals, the acute oral or dermal LD_{50} is 10 - 200 mg/kg.
- The multiple exposure lethal dose is 50 - 70 mg/kg. Minimal toxic daily doses of 20 - 35 mg/kg in calves.
- Young swine have died following exposure to oily, freshly treated wood used in farrowing crates or farrowing houses.
- Toxic to fish at 30 - 300 ppb and fish kills have resulted from spills into lakes and streams, primarily after a rain has flushed pentachlorophenol from an area used in wood treatment into the body of water.
- LC_{50} in the feed of birds is 3400 - 5200 ppm.
- Rats tolerate feed containing 1000 ppm (approx. 50 mg/kg) for 90 days but develop moderate hepatocellular necrosis and interstitial fibrosis. The no-effect feed concentration in rats was 25 - 50 ppm in the diet (1.5 - 3.0 mg/kg).
- **Contaminants:**
  - Many studies evaluating the toxicity of pentachlorophenol must be evaluated with the knowledge that chlorinated dibenzodioxin or chlorinated dibenzofuran contaminants (although often present in varying amounts) were neither quantitated nor considered in the interpretation of the data. These dioxins and dibenzofurans tend to be far more toxic than the pentachlorophenol itself in most cases. Subacute or chronic toxicity is often dependent upon the nature and extent of contamination of the particular batch of pentachlorophenol in question.
  - When calves were fed pentachlorophenol at 15 - 20 mg/kg/day with varying degrees of contaminants present, depression in body weight gains were proportional to the concentrations of contaminants contained. Signs first developed after 8 weeks.
  - At high doses contaminants are embryotoxic or fetotoxic, but purified pentachlorophenol itself is reportedly not teratogenic.
  - Pentachlorophenol contaminants include various isomers of hexa-, hepta-, and octachlorodibenzodioxin, various dibenzofurans, hexachlorobenzene, and other compounds such as tetrachlorophenols. Of these, the hexachlorodibenzodioxins are of greatest concern and this group of compounds is now believed to have caused chick-edema disease from feeding the birds a ration containing waste oils originating at a leather processing plant.
  - The super-toxic, 2,3,7,8-tetrachloro-dibenzodioxin, which is the principle dioxin of concern in some of 2,4,5-T used to formulate Agent Orange and of concern in such areas as Times Beach, MO, and Love Canal, NY, **has never been detected** in any significant concentration in pentachlorophenol preparations.
  - Apparently, Dow Chemical Co. developed a process to make a much cleaner (far less dioxin-containing) pentachlorophenol and offered the technology to all producers of the pesticide. They were supported neither by their colleagues in industry, nor by the EPA, in spite of the fact that the increased cost would have been only pennies per gallon. Dow went ahead and manufactured their product with the new technology, but because their product was slightly more expensive Dow is no longer in the pentachlorophenol business.
  - Air concentrations of 1 mg/m^3 cause respiratory tract inflammation.

Absorption, Distribution, Metabolism and Excretion (ADME)

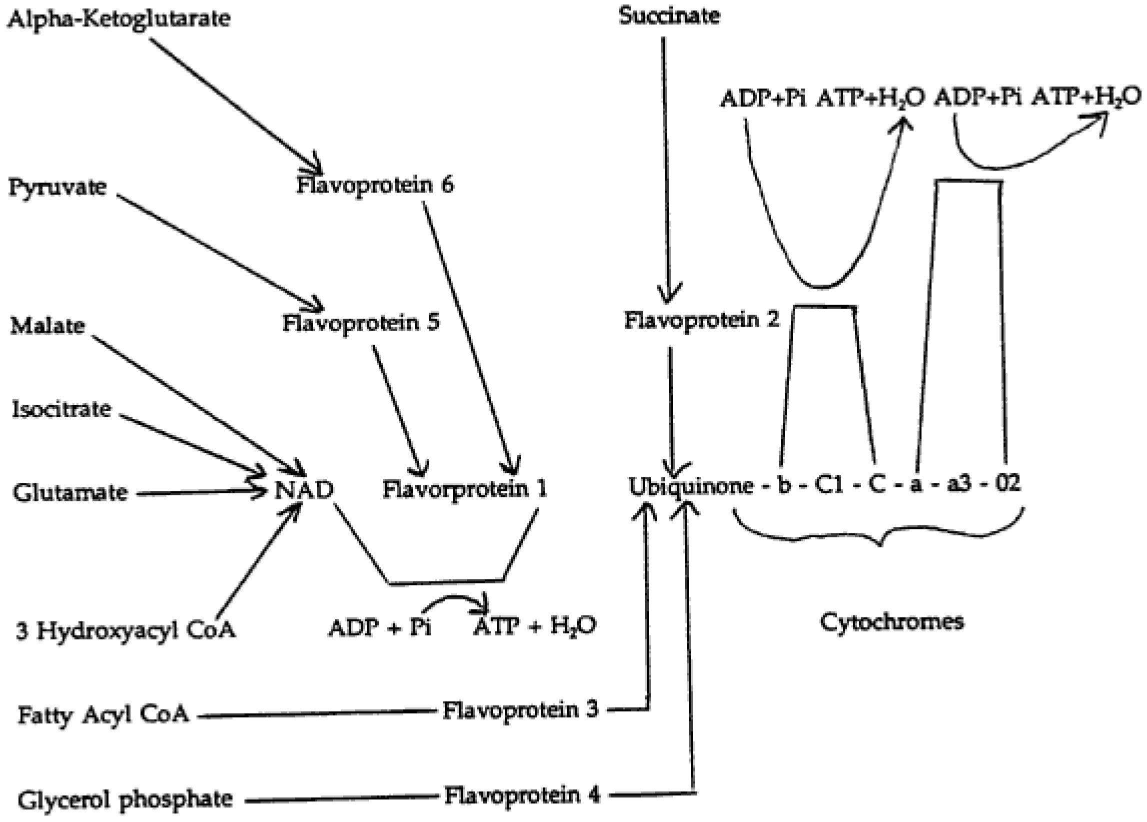
- Rapid absorption from the skin, digestive tract and lung. Peak blood concentrations are reached within a few hours of ingestion.
- With a constant level of intake, blood concentrations generally plateau in five days.
- Most pentachlorophenol is in the plasma, with only small amounts in red blood cells.
- The highest tissue concentrations are in liver and kidney.
- Eliminated in the urine of all species tested and has a half-life of 1.5 - 2 days.
- Metabolites include tetrachlorohydroquinone and glucuronide conjugates; although some free pentachlorophenol is eliminated in the urine.

Mechanism of Action

- The acute toxicity of pentachlorophenol-containing products is primarily a result of the pentachlorophenol itself, which uncouples oxidative phosphorylation. Uncoupling of oxidative phosphorylation by pentachlorophenol appears to be due to the chlorophenate ion. By "uncoupling" the transfer of electrons down the cytochromes from the actual mitochondrial production of ATP, there is rapid utilization of the body's energy stores.

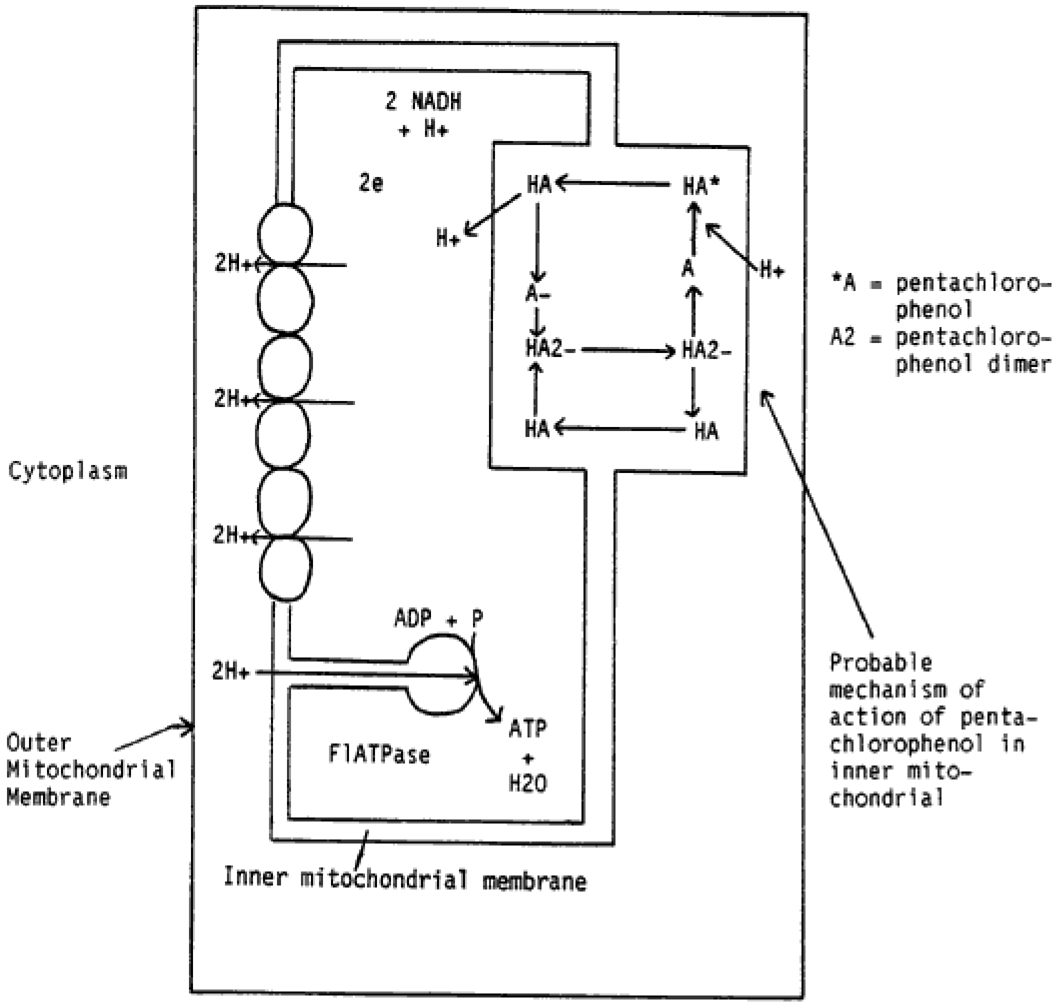
- It has also been suggested that there are inhibitory effects on enzymes, such as cellular kinases, dehydrogenases and reductases.
- The effects of the halogenated dioxin and dibenzofuran contaminants will be discussed in a subsequent section.

Normal Function: Sources of Electrons and Components of the Electron Transport Chain



Mechanism of Pentachlorophenol

Probable Sites of Energy Conservation in the Respiratory Chain: This process actually depends upon H^+ (proton) pumping. As electrons pass down the cytochrome chain, hydrogen ions are pumped from inside the inner mitochondrial membrane to between the inner and outer membranes. This proton gradient drives FlATPase. The gradient is destroyed by ferrying of protons by pentachlorophenol which alternates from dimer to monomer as it carries protons.


2 NADH
+ H+
2e
HA
HA*
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A
H+
A-
HA2-
HA2-
HA
HA
2H+
2H+
2H+
Cytoplasm
ADP + P
2H+
ATP
+
H2O
F1ATPase
Outer
Mitochondrial
Membrane
Inner mitochondrial membrane
*A = pentachlorophenol
A2 = pentachlorophenol dimer
Probable mechanism of action of pentachlorophenol in inner mitochondrial

Signs

- When cows received technical grade penta, they became unthrifty after 8 weeks and, at 160 days, had dry scaly skin, diarrhea, urethritis, cystitis and a normocytic, normochromic anemia.
- With respiratory exposure, pain in the respiratory tract is accompanied by sneezing and coughing. Acclimated humans will tolerate up to 2.4 mg/m^3.
- Mild toxicoses:
  - Weakness.
  - Anorexia.
  - Lethargy.
- Moderate toxicoses.
  - Rapid respiratory rate.
  - Hyperpyrexia (106 - 108 ºF) and possible hyperglycemia, and glycosuria.
  - Diaphoresis (sweating) in capable species.
- Lethal toxicoses.
  - The above listed signs.
  - Cardiac and skeletal muscular collapse and death.
  - Rapid onset of rigor mortis.
  - Renal damage may result in proteinuria and increased blood urea nitrogen.
- Chronic toxicoses.
  - Anemia.
  - Dependent upon contaminants and may include weight loss, poor growth, dry scaly skin, diarrhea, and urethritis/cystitis.

Lesions

- Local irritation of areas contacted by the pentachlorophenol.
- Pulmonary edema and congestion.

- Hepatic enlargement, centrilobular degeneration and fatty change.
- Renal tubular hydropic and fatty change.
- Cattle: (nonlethal dose of 15 - 20 mg/kg, technical pentachlorophenol)
    - Reduction in splenic white pulp (nonspecific change reflecting stress, similar to lesions of acute viral infection).
    - Bile duct hyperplasia, and no other hepatic changes noted.
    - Villous hyperplasia of the mucosa of the urinary bladder (severe).
    - Hyperkeratosis of the skin (probably largely dependent upon contaminant concentrations).

Diagnosis

- A background blood pentachlorophenol determination in control animals revealed levels of 130 ppb.
- Clinical signs of pentachlorophenol toxicosis generally occur when blood concentrations are from 40 - 80 ppm. Acute lethal toxicoses occur with blood concentrations of 100 ppm and tissue of 200 ppm.
- Blood concentrations of 2 ppm or less are not associated with clinical signs. Also concentrations of 10 - 300 ppb in the blood are common in animals in barns built in part with penta treated wood but are not associated with clinical signs.
- Blood concentrations of 33 - 87 ppm in cattle fed 15 - 20 mg/kg/day of technical pentachlorophenol were associated with mild to moderate toxicoses at 160 days of dosing.
- In cattle fed technical penta at 15 - 20 mg/kg/day, liver chlorodioxin concentrations after 160 days were 29, 1057, and 3456 ppb for the hexa, hepta, and octa isomers, respectively.
- Immunologic effects may include a reduction in immunoglobulins.

Treatment

- Terminate exposure: May include the use of bedding materials to remove animals from surfaces bleeding penta and resulting in dermal exposure; avoidance of contact of feed with penta-treated surfaces; control of interior temperature to reduce volatilization from warm areas; consider increased ventilation or removal of animals if extremely high concentrations or toxic effects are already present.
- Bathe off any exposed surfaces with a dish detergent.
- For early ingestions, the use of an emetic, activated charcoal and a cathartic are likely to be of value. For higher doses, lavage, including enterogastric or rumen lavage, may be appropriate depending upon the species and time factors involved.
- Correct acidoses if present with bicarbonate in fluids.
- Correct dehydration and promote excretion of pentachlorophenol and conjugates by the administration of fluids.
- Maintain positive energy balance to combat energy losses due to the biochemical effects of pentachlorophenol and to allow hepatic conjugation of the pesticide.
- Minimize stress and control any environmental conditions which may result in physiological increases in body temperature, stressors these have previously been shown to increase the likelihood of acute toxicoses with other uncouplers of oxidative phosphorylation.

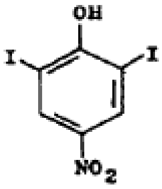
Disophenol

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Fevers
Most species	Hours	Days for most compounds; often lethal	

Sources

- Disophenol (DNP®, or 2,6-diiodo-4-nitrophenol) is administered to dogs and cats as an anthelmintic to eliminate hookworms. The product is a yellow, injectable solution
- DNP® is supplied commercially as a 4.5% solution (45 mg disophenol/ml) in a water/polyethylene glycol vehicle for administration by subcutaneous injection.
- A routine therapeutic dose of disophenol for dogs is 10 mg/kg.
- Similar anthelmintic formulations include Ancylol® and Syngamix®.

- Disophenol is used to remove gapeworms (*Syngamus trachea*) from turkey poults. The gapeworm formulation is given in the feed or in capsules.
- The dose for turkey poults given in the feed is 3.5 mg/lb body weight.



Disophenol

Toxicity

- Disophenol has approximately a 3-fold margin of safety in the dog and cat, when administered subcutaneously. Generally animals may respond to an apparent stinging sensation immediately after injection.
- It is reported that puppies as young as 2 days of age may be given the drug without adverse effects, except that occasional opacity of the lens is seen at less than 4 months of age.
- Reportedly, there are no side effects in pregnant animals, regardless of the stage of gestation.
- Disophenol has been recommended for severely parasitized animals.
- LD_{50} values in male rats:
    - Oral 170 mg/kg.
    - IV 105 mg/kg.
    - IP 105 mg/kg.
    - SC 122 mg/kg.
- LD_{50} values in male mice:
    - Oral 212 mg/kg.
    - IV 88 mg/kg.
    - IP 107 mg/kg.
    - SC 110 mg/kg.
- In acute toxicity studies the minimum lethal oral dose was between 100 and 200 mg/kg. Single injectable doses of 30 mg/kg were safe, but doses above 36 mg/kg were lethal (Wood et al., 1961).
- There is evidence to suggest that elevation of body temperature may increase susceptibility of an animal to acute toxicosis. Exposure to high environmental temperatures or vigorous exercise is therefore contraindicated after disophenol administration. Large breeds with heavy coats may be predisposed to toxicosis in the summer, due to inherent thermoregulatory difficulty.

Mechanism of Action

Uncouples oxidative phosphorylation in a manner probably like that associated with pentachlorophenol. The energy-releasing processes of the cytochrome chain are disconnected (uncoupled) from the energy-requiring endergonic processes that form ATP and apparently much of the free energy is dissipated as heat.

Absorption, Distribution, Metabolism and Excretion (ADME)

- The half-life of DNP is reported as 9 - 15 days.
- Because of the comparatively long half-life, retreatment is not recommended within 21 days.
- In chronically dosed dogs, a dose 1.6 times the recommended dose (i.e., 16.5 mg/kg SC) once a week for 8 weeks was not toxic to healthy dogs; while a lower than recommended dose (7.5 mg/kg), if repeated daily was lethal in 6 days. Lower doses (5.0 mg/kg) repeated daily in dogs did not cause overt toxic effects when administered for 60 days.

- Signs are associated with an increased metabolic rate with cellular energy depletion and include tachycardia, polypnea, hyperthermia, and early *rigor mortis* in fatal cases.
- Lenticular opacity of varying severity is likely to occur in adults (as well as in young dogs) given higher than recommended doses of disophenol.

- At least in young puppies given the recommended dose, the lenticular opacity is not severe and regresses within 7 days.
- Vomiting is another sign of acute toxicosis, dehydration is slight to moderate.
- In acute toxicosis, death is believed to result from direct circulatory depression, hyperpyrexia, acidosis and anoxemia. Hyperventilation is common, in addition to the polypnea mentioned above. Pyrexia may commense from 1 - 6 hours after dosing, and, in survivors, it may cease after 40 hours.

Clinical Pathology

- High packed cell volume, neutrophilia and lymphopenia occurred in a clinical case of disophenol toxicosis.
- Congestion and hydropic degeneration of the lungs and liver, and fatty degeneration of the myocardium were reported in dogs with acute disophenol toxicosis.
- Only one report of a disophenol-poisoned dog involved evaluation of blood pH and consistent changes were not apparent in that animal.

Treatment

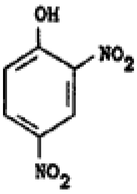
- Fluids, such as lactated Ringer's with bicarbonate may be indicated.
- Ice packs.
- Very limited investigation of the antipyretic, dipyrone, indicated that the drug may be of benefit. However, the results were not statistically significant and, in view of the peripheral mechanism of heat generation in pentachlorophenol toxicosis, a logical basis and confidence in success with the use of dipyrone is lacking.
- Animals should not be stressed in order to avoid increasing the body temperature.
- An attempt should be made to maintain a positive energy balance in the affected animal (provide dextrose, food, etc.).
- In instances of accidental overdose, in which it is recognized immediately after injection that a large overdose (in the neighborhood of 3-fold or greater) has been given, actual excision of the subcutaneous tissue underlying the injection may be indicated to save the animal's life. There is no data on the rate of absorption of disophenol from the subcutaneous injection site and therefore the benefit of this approach remains to be substantiated.
- Halothane anesthesia should be avoided due to its tendency to cause malignant hyperthermia.

Dinitrophenol and Other Uncouplers of Oxidative Phosphorylation

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Fevers
Most species	Hours	Days for most compounds; often lethal	

Sources

- Various dinitro derivatives of cresol and phenol are used as insecticides acaricides, fungicides, and herbicides (nonselective biocides). They are applied in sufficient amounts to wet the target organism for contact action. Included in these compounds are: dinitrophenol (2,4-dinitrophenol, an insecticide, acaricide, fungicide which is phytotoxic to green plants); dinoseb (DNBP, Dinitro®, Basanite®, Dow General Weed Killer®, and several other products used as a herbicide, dessicant or dormant fruit spray); DNOC (dinitrocresol); DNAP (Dinosam®, a rarely encountered herbicide); and 5 DN-111, a discontinued product.
- Animals may be seriously exposed from entering treated fields, or by contact with concentrated forms of these pesticides.



Dinitrophenol

Toxicity

- The LD50 of dinitrophenol in the rat is 0.027 - 0.10 mg/kg.
- The acute oral LD50 of dinoseb in the rat is 40 - 60 mg/kg.
- The acute oral LD50 of DNOC in the rat is 20 - 50 mg/kg.

Absorption, Distribution, Metabolism and Excretion (ADME)

Dinitrophenol is about twice as toxic as disophenol on a single dose basis, but is less toxic on a repeated basis, indicating that it is not as cumulative as disophenol.

Mechanism of Action

Uncouples oxidative phosphorylation, presumably by the same mechanism as that of pentachlorophenol.

Treatment

See Pentachlorophenol and Disophenol handouts.

Other Uncouplers of Oxidative Phosphorylation

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Fevers
Aspirin (See Toxicants that Cause Acidosis)	Most species	Hours	Days for most compounds; often lethal	
Bromethalin (See Toxicants Associated with Mixed Effects on the CNS)	Most species	Hours	Days for most compounds; often lethal	
Hexachlorophene (See Toxicants Associated with Mixed Effects on the CNS)	Most species	Hours	Days for most compounds; often lethal	

- Other agents, some previously mentioned which **may** uncouple oxidative phosphorylation to a clinically significant degree in some instances of toxicosis include:
  - Pentachlorophenol
  - Disophenol
  - Other chlorophenols
  - Aspirin
  - Hexachlorophene*
  - Bromethalin*

*Hexachlorophene is known to cause fevers in animals exposed to high doses and both hexachlorophene and bromethalin seem to cause primary effects on myelin of the central nervous system (see other sections for details).

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Fevers
Halothane	Swine, dogs (esp. greyhounds)	Minutes to hours	Hours; often lethal	
Garbage toxicosis	(See Bacterial Toxins that Affect the GI Tract)			
Any Syndrome with seizures or exertion	(See Toxicants Associated with Stimulation or Seizures)			

Section VI: Toxicants that Affect the Kidneys

Introduction to the Toxicology of the Urinary System

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Introduction to the Toxicology of the Urinary System

1. **Major Functions of the Urinary System**
    - Elimination of waste products from the body
    - Regulation of the volume of the extracellular fluid
    - Control of electrolyte concentrations in the extracellular fluid
    - (e.g. Na^+, K^+, Ca^{++}, Cl^-)
    - Control of acid base status (pH)
    - Production of hormones
        - Erythropoietin (stimulates red blood cell production - bone marrow)
        - Vitamin D_3 [kidney hydroxylates (addition of an -OH group) to activate]
        - Renin
            - With a decline in blood pressure, the kidney secretes renin which is an enzyme that acts on a plasma globulin to produce angiotensin. Angiotensins include a potent vasoconstrictor. Angiotensins also stimulate aldosterone secretion from the adrenal glands. Aldosterone increases sodium retention, which attracts water to the extracellular fluid, thereby expanding the plasma volume and thus, increasing the blood pressure.
        - Vasoactive prostanoids and kinins

2. **Major Clinical Effects of Kidney Failure**
    - Increased concentrations of waste products in the body
    - (e.g. increased blood urea nitrogen, increased serum creatinine)
    - People and other animals may appear weak, vomit, develop an odor to the breath, oral ulceration
    - With severe acute renal failure, renal shutdown (absence of urine production) may occur
    - With chronic renal failure, increased urine production (decreased concentrating ability) and associated thirst may occur
    - Dilute urine (low specific gravity) often containing amino acids, protein and sometimes glucose.
    - Potential anemia with chronic renal failure

3. **Sites and Mechanisms of Action of Urinary Tract Toxicants**
    - Sites of action may include (epithelial cells &/or basement membranes of):
        - Glomeruli (e.g. doxorubicin; aminonucleoside of puromycin)
        - Renal tubular epithelial cells (often proximal tubules are involved) (e.g. ethylene glycol toxicosis)
        - Collecting ducts (e.g. phenylbutazone toxicosis - renal papillary necrosis)
        - Lower urinary tract [e.g. carcinogenesis from toxins in *Pteridium* (= bracken fern)]
    - Toxic effects on cells range from imperceptible to necrosis
    - Reactive oxygen species
        - Reactive oxygen species and their generation: all can produce lipid peroxidation
            - Are often produced by neutrophils (often involved in glomerular nephritis - e.g. phorbol ester toxicosis; bacterial infections)
            - Generated by reperfusion injury (e.g. after relief of circulatory shock - caused by any of the following: hemorrhage, sudden cardiac failure, acute anaphylaxis, bacterial toxins, other toxic chemicals that affect the gut, heart, vasculature)
            - Superoxide anion (O^-)= the free radical produced when oxygen accepts one electron
                - May diffuse through the cell, but cannot readily cross membranes
                - Often reacts within membranes

            - Hydrogen peroxide (H_2O_2) = a reactive neutral molecule produced when oxygen accepts two electrons
                - Readily crosses membranes
            - Superoxide anion reduces Fe^{+3} to Fe^{+2}, and Fe^{+2} reduces H_2O_2 to the hydroxyl radical (• OH).
                - Extremely reactive, reacts before diffuses or crosses membranes
                - Reacts in cytosol
        - Effects of reactive oxygen species:
            - Induction of a chain reaction resulting in propagation of lipid peroxidation (altered membrane fluidity and permeability)
                - Decomposition of lipid peroxides is catalyzed by transitional metals; but this forms alkoxy and peroxy free radicals that propagate the reaction
            - Inactivation of cellular enzymes by directly oxidizing critical -SH or $-NH_2$ groups - results in altered enzyme activity
            - Depolymerization of polysaccharides
            - Induction of breaks in DNA
            - Production of toxic breakdown products from lipids including:
                - Hydroxylated fatty acids
                - Alkanals
                - Alkenals
    - Altered calcium homeostasis
        - Extracellular Ca^{++}: intracellular Ca^{++} is normally 10,000:1
        - Proximal renal tubules normally reabsorb 60 - 70% of filtered Ca^{++}
        - Must avoid elevated intracellular free Ca^{++} to avoid:
            - Activation of calcium-dependent phospholipases
                - Degrade cellular organelles
                - Degrade plasma membrane phospholipids altering function
                - Uncouple oxidative phosphorylation
                - Cause marked disorganization of the cytoskeleton
                - Cause apoptosis &/or necrosis
        - Causes of elevated intracellular Ca^{++}:
            - Reperfusion injury (lack of ATP to pump Ca^{++} out of cells)
            - Mercuric chloride (one factor in the toxicosis)
            - Gentamicin (antibiotic) (one factor in the toxicosis)
    - Glomerular effects of urinary toxicants
        - May complex with, alter permeability of, or partially occlude renal glomerular capillaries
        - Altered permeability may result in an increased loss of protein
    - Tubular effects of urinary toxicants
        - A number of toxicants damage the proximal renal tubular epithelial cells
        - Some nephrotoxicants damage the basement membrane making effective regeneration (healing) less likely
        - A few nephrotoxicants may precipitate in and thereby block the renal tubules
    - Vascular effects of urinary toxicants
        - Vasospasms or swelling in kidney may greatly impede renal blood flow
        - Reduced renal perfusion is a common complicating factor in a number of forms of toxicant-induced kidney failure

4. **Specific Nephrotoxic Substances and Their Primary Effects**
    - Heavy metals
        - Alter -SH and other groups in proteins
        - End product of acute (high dose) exposure to many metals include damage to proximal tubular epithelial cells (necrosis with loss of protein) with marked deprivation of blood flow (combination of direct cellular toxicity and ischemia)
        - Lead (Pb^{++})
            - Lead (Pb^{++}) may not only affect -SH groups, but may also alter Ca^{++} homeostasis
            - Lead sequestered in intranuclear inclusion bodies as a lead/protein complex
        - Mercury (Minamata Bay Disease)
            - Several forms of mercury were once used as diuretics
            - (Elemental, inorganic, organic)

    - Mercury salts are most nephrotoxic
    - Breakdown of organic forms to inorganic forms seems to account for their nephrotoxicity.
    - Mitochondrial enzymes are especially sensitive to Hg (potential role of Ca^{++} disruption yet to be thoroughly investigated)
    - Causes glomerular and tubular injury
      - Glomerular damage believed linked to a Hg-induced autoimmune reaction
      - Outer proximal tubules are most sensitive
      - With higher doses, injury proceeds toward the medulla
  - Cadmium (Itai-Itai Disease)
    - Stimulates synthesis of metallothionein to which it binds
      - Metallothionein complex limits effects of Cd on some organs such as the testis
      - Metallothionein complexes in kidney can lead to such high concentrations that eventually the kidney becomes damaged
      - Cause of chronic renal failure
      - Multiparous women most susceptible - osteoporosis - spontaneous fractures - Itai-itai = ouch-ouch disease.
- Ochratoxin-A (Balkan nephropathy of human beings; porcine nephropathy)
  - Mycotoxin from several species of *Penicillium* and *Aspergillus*
  - Selectively taken up by the kidney
  - Affects rural populations of Bulgaria, Romania, and Yugoslavia
  - Causes marked interstitial fibrosis, proximal tubular injury
  - Also immunosuppressive
  - Urinary tract carcinogen
  - Residues - especially from grain, lesser amounts from kidneys and blood (blood pudding)
- Cephalosporin antibiotics
  - Nephrotoxic in rats and human beings
  - Actively transported from the peritubular capillary into the tubular epithelial cell, but not efficiently across into the tubular lumen
  - Damages proximal tubules
  - Induces production of reactive oxygen species
  - Inhibits mitochondrial energy production
- Cyclosporine
  - Fungal cyclic polypeptide used to limit rejection after organ transplantation
  - Renal effects are expected with the routine use of the drug
  - Multiple types of lesions may develop in the kidney potentially involving the glomeruli, proximal tubules, and vasculature.
  - Interstitial fibrosis can lead to a progressive form of worsening kidney failure (fibroplasia - contraction - necrosis - more fibroplasia - etc.)
- Paraquat
  - At massive doses, paraquat damages not only the lung, but also the kidney
  - Kidney damage delays the rapid renal elimination of paraquat that occurs at lower doses thereby increasing the severity of lung damage
- Nonsteroidal anti-inflammatory drugs
  - Induce "analgesic nephropathy"
  - Several such drugs may cause papillary necrosis (e.g. phenylbutazone; aspirin)
    - This effect is believed to be related to inhibition of prostaglandin synthesis by the non-steroidal compound) and locally impaired blood flow
  - May also affect proximal tubules, probably by an independent mechanism
    - May require higher doses than those necessary to have a threshold effect in the renal papilla

Nephrotoxic Metals and Inorganics

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Cadmium

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Metals and Inorganics
Most species	Days to weeks	Weeks to permanent damage; potentially lethal; toxicosis is rare	

Sources

- Artists' paints.
- Cadmium is a metal which has become an environmental contaminant as a result of effluents from plants smelting zinc, copper and lead, as well as from industries using cadmium in batteries, alloys and paints. Environmental contamination is very important since cadmium is one of the most biocumulative metals.
- Cadmium (and lead) are often components of municipal sewage sludge in many communities in which the appropriate industries are located. This sewage sludge has, at times, been sold or given away as a soil amendment for agricultural or home gardening applications. Commercial sludge may contain up to 1500 mg of cadmium per kg dry material.
- Cadmium added to soil tends to be taken up into the leafy portions of plants, but may sometimes reach toxic concentrations in grains as well.
- Cadmium-containing fungicides were once used on turf grass. Cadmium chloride was sometimes used for this purpose, a concentrated form of which contained 12.5% elemental cadmium. Trade names included Caddy® and Vi-Cad®.
- Cadmium succinate was also used on turf grass as a fungicide and the concentrate contained 29% elemental cadmium. The trade name was Cadminate .
- Other turf grass fungicides contained mixtures of cadmium, calcium, copper, zinc and chromates. Trade names included Miller 531®, and Crag Turf Fungicide 531®.

Toxicity

- A rat oral LD_{50} of cadmium chloride was 88 mg/kg.
- A rat oral LD_{50} of cadmium succinate was 660 mg/kg.
- Long-term effects of low-level exposure to cadmium include renal tubular disease, chronic obstructive pulmonary disease, and emphysema. Respiratory effects have been noted following inhalatory exposure.

Mechanisms of Action

- Cadmium inhibits enzymes associated with zinc and displaces it from metalloenzymes. Cadmium also inhibits zinc uptake by the male reproductive tract.
- Chronic cadmium toxicosis causes increased likelihood of copper and iron deficiencies, blocks renal synthesis of the active form of vitamin D, and results in anemia, growth inhibition and poor bone mineralization.
- Low levels of dietary protein, calcium, iron, or zinc cause increased cadmium absorption. Young absorb more than adults.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Two to 8% of ingested cadmium is absorbed on a chronic exposure basis, and a fraction of the absorbed cadmium is initially retained in the liver and then redistributed, especially to the kidneys.
- The absorbed cadmium is eliminated in the feces via the glands of the stomach, intestine and pancreas.

- Cadmium induces metallothionein, a metal binding protein. Metallothionein also binds zinc, copper, and iron. Metallothionein binds cadmium to protect organs from exposure to the metal, but the Cd-metallothionein complex is taken up by the kidney, and this enhances nephrotoxicity.
- After large amounts accumulate in the kidneys, renal damage occurs and only then does urinary excretion result and the renal concentration falls.

Clinical Signs

- In chronic exposure in man, renal damage, bone deformities, osteoporosis, spontaneous fractures and anemia occur.
- Cause of itai itai (translation, ouch, ouch) disease in Japan. This disease was associated with the ingestion of cadmium-contaminated rice and is characterized by acute pain and deformity from spontaneous fractures. Women (especially those which had several children) were more susceptible.
- Acute oral exposure to high concentrations may cause excessive salivation, persistent vomiting, diarrhea, abdominal pain, ataxia, loss of consciousness, severe gastroenteritis, subdural hemorrhage and testicular necrosis.
- Inhalation of cadmium is generally characterized by dyspnea, cough, fever, and pulmonary edema.

Diagnosis

- Liver, kidney, and/or blood calcium.
- Horses tend to have much higher cadmium (in normal animals) than with other domestic species.
- Appropriate history, clinical signs, histologic changes in the kidneys, bone, gut, etc.

Treatment

- For acute toxicoses, BAL and calcium EDTA decrease mortality, **but for chronic toxicoses** are generally **ineffective and may increase cadmium concentrations in the kidney,** BAL **is considered contraindicated after chronic exposure** due to increased risk of nephrotoxicity.
- Efforts to remove cadmium from the digestive tract should be employed in recent exposures.
- In cases of chronic exposure, supplementation with zinc, copper and iron in more than normally adequate amounts are significantly protective. Vitamins C and D, cysteine and selenium also aid in protection. Naturally, steps to terminate exposure should be instituted.

Comment

Cadmium is rarely recognized as a toxicant in veterinary practice.

Zinc

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Metals and Inorganics
Dogs, seals, caged birds, ostriches	Days	Days to permanent damage; often lethal	

Sources

- Zinc toxicoses have recently been reported in dogs as a result of ingestion of zinc nuts from hardware used on transport cages or those in veterinary facilities or from repeatedly licking off zinc oxide ointment (often Desitin) used to treat skin lesions.
- Ingestion of pennies.
    - **Note** - Pennies minted beginning in 1983 (and some from 1982) contain 99.2% zinc and 0.8% copper by weight (pennies weigh 2.5 grams each).
- Poisoning reported in human beings and animals from drinking water (especially when it's acidic) from galvanized tanks. Poisonings have been reported as a result of ingestion of acidic food or beverages from galvanized containers.
- Birds may ingest zinc from "welded wire" fencing.

- "Metal fume fever" reported to occur in industrial workers exposed to zinc vapors. This syndrome is characterized by pulmonary manifestations, fever, and gastroenteritis.

Susceptible Species

Poisonings described in dogs, cats, ferrets, mink, sheep, horses, cattle, caged birds, and ratites.

Toxicity

- Zinc at 500 - 1,500 ppm in diets fed to ferrets resulted in diffuse nephrosis; and 3,000 ppm dietary zinc was lethal.
- An acute oral LD_{50} for zinc chloride was 96 mg/kg in the guinea pig.
- Rats, pigs, and poultry tolerate dietary levels of 1,000 to 2,000 ppm without adverse effects.
- Cattle and sheep have decreased feed consumption when the diet exceeds 1,000 ppm zinc.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanism of Action

- Zinc is excreted primarily via the bile and pancreas.
- Chronic zinc toxicosis interferes with absorption and utilization of iron and copper.
- Mucosal irritation can result from ingestion of certain zinc salts (e.g., zinc oxide).
- Approximately 2/3 of the zinc in serum or plasma is loosely bound to protein and the remainder is tightly bound.

Clinical Signs

- Single ingestions of zinc oxide ointment are characterized mainly by vomiting.
- Subacute or chronic zinc toxicosis primarily affects the renal, hepatic, and hematopoietic tissues.
- The most common clinical signs in small animals include: vomiting, depression, anorexia, hemoglobinuria, diarrhea, weakness, icterus. Can also see clinical signs (e.g., oral ulcers) associated with acute renal failure.
- Cattle may present with anorexia, depression, polydipsia, polyphagia, decreased milk yield, chemosis, exopthalmia, convulsions, and death.

Clinical Pathology

- Regenerative anemia; hemolytic anemia with hemoglobinemia and hemoglobinuria possible.
- Increased serum alkaline phosphatase, bilirubinemia.
- Hypophosphatemia, isosthenuria or hyposthenuria, proteinuria, hematuria, azotemia, and renal casts all consistent with acute renal failure.
- Lesions.
    - Hemorrhagic gastritis.
    - Proximal renal tubular epithelial necrosis.
    - Centrilobular hepatocyte vacuolization, necrosis of individual cells occurs. Bile casts in bile canaliculi.

Diagnosis

- Elevated serum, tissue (kidney, liver), and urine zinc concentration. Note: Special tubes for elemental analysis (Royal blue top) are recommended. In addition, syringes used in collecting blood should contain no rubber gromets (i.e., all glass or all plastic). This is necessary because certain blood tubes and syringes have zinc stearate present in the lubricant which can contribute up to 5 - 6 ppm extraneous zinc.
- Radiograph abdomen for presence of zinc hardware.
- Differential diagnosis-acute autoimmune hemolytic anemia.

Treatment

- Symptomatic and supportive therapy.
- Fluid for acute renal failure.

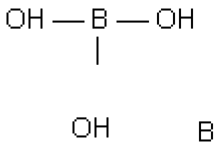
- Emetic if no contraindications exist.
- Gastrotomy or enterotomy may be required to remove zinc foreign bodies.
- Chelation therapy (CaEDTA or penicillamine) may be required.
- Give fluids and bicarbonate (slow IV) to help prevent renal failure if hemolysis is a problem. Blood transfusions may be indicated.

Boric Acid and Borate

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Metals and Inorganics
Mostly pets	Hours to days	Days to weeks; toxicosis rare; deaths very rare	

Sources

- Roach and ant poisons, which are often > 95% boric acid (often called ortho-boric acid), comprise the most common source causing toxicosis in small animals.
- The decahydrate of sodium borate (borax) is used in cleaning clothing in washing machines.
- Sodium perborate, which decomposes to form hydrogen peroxide and sodium borate, is found in denture cleansers.
- Whether sodium borate breaks down to boric acid is unknown.



$B(OH)_3$

Boric Acid

$B_4Na_2O_7$

Sodium Borate = Sodium Tetraborate

Toxicity

- Boric acid-oral LD_{50} in the rat is 2.68 g/kg to 4.08 g/kg.
- Borate-oral LD_{50} in the rat ranges from 4.5 - 4.98 g/kg.
- One gram of boric acid is roughly equivalent to 1.55 g borax.
- Sodium borate contains 21.50% boron.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanism of Action

- Exact mechanism is unknown; generally cytotoxic to all cells.
- Soluble borates are absorbed from the gastrointestinal tract.
- Concentrated in the kidney before excretion; probably related to the fact that the kidney is the organ that is most damaged. Renal excretion is comparatively slow.

Signs

- Vomiting, diarrhea, anorexia.
- Muscle weakness and ataxia, possible hyperpyrexia.
- Seizures possible, tremors may be seen prior to seizures if they occur.
- Depression and lethargy.
- Oliguria or anuria, possibly hematuria, and albuminuria.
- Erythematous skin eruptions develop in humans (and pet monkeys) which may become generalized; may have a "boiled lobster" appearance.
- Metabolic acidosis may occur.

Lesions

Gastroenteritis, nephrosis, fatty degeneration of kidneys, hepatic damage, fatty degeneration of liver, possible cerebral edema.

Diagnosis

- Appropriate clinical signs and/or lesions with a history of sufficient exposure.
- A bench chemistry test is available for detecting boric acid in urine.
- Oliguria, anuria, proteinuria, casts and red blood cells.
- Chronic poisoning can occur.

Treatment

- For recent exposure, an emetic has been recommended or, if contraindicated, gastric lavage is suggested, either approach is followed by activated charcoal administration.
- Fluid diuresis, peritoneal dialysis, and/or exchange transfusions.
- Peritoneal dialysis has been shown to be effective in reducing blood levels of boric acid in human poisoning.
- Symptomatic treatment as necessary.
- Should seizures occur in dogs, diazepam is recommended.

Other Nephrotoxic Metals

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Metals and Inorganics
Calcium	Poultry (nonlayers)	Chronic	Chronic; often lethal	
Mercury	(See Toxicants with Mixed Effects on the Nervous System)			
Copper	(See Toxicants that Cause Hemolysis)			
Phosphorus	(See Toxicants that Affect the Liver)			
Uranium	(Toxicosis is rare)			
Bismuth	(Toxicosis is rare)			
Chromium	(Toxicosis is rare)			

Sources

- **Mercury**: See section on Mercury under the heading Toxicants with Mixed Effects on the Nervous System.
- **Copper**: Will be discussed in the section on agents causing hemolysis. The renal effects of copper are mediated in significant measure as a result of the effects of hemoglobin on the renal tubules. In short copper builds up in the liver until a critical concentration exists, then, usually after some external stress, liver failure and loss of the copper stored in the liver result in massive release of copper into the blood. The resultant hemolysis causes hemoglobinemia, which produces a tubular nephrosis and gun-metal colored kidneys. Hemoglobinuria occurs and death is very common. By far, sheep comprise the most commonly affected species. The veterinary diagnostician considering copper toxicosis must remember the hepatotoxic, hemolytic, and nephrotoxic effects of chronic copper toxicosis as well as the possibility of gastrointestinal damage from acute exposure.
- **Uranium**: Acute renal damage may result when soluble uranyl ions are absorbed after oral ingestion or when uranyl nitrate is absorbed through damaged skin.
- **Chromium**: Sources include corrosion inhibitors, paints, drilling muds used in oil well exploration, inks and wood preservatives. Ashes from some treated lumber products may also be a source, although the primary toxicant in such cases is usually arsenic. Acute toxicosis is characterized by gastrointestinal irritation with ulceration, shock, liver injury and renal damage with tubular necrosis and albuminuria. Toxicosis may result from accidental mixing of chromium containing materials into feeds.

- **Bismuth**: The toxicity of most bismuth containing compounds available to animals is low. With massive doses, bismuth causes effects much like some of those caused by mercury: gingivitis, dermatitis, and kidney damage. As in the case of mercury poisoning, toxicosis due to bismuth may be treated with the chelator BAL. Commonly encountered bismuth containing medications include Pepto-Bismol®, which contains bismuth subsalicylate, but the primary concern with this product is due to salicylate, not bismuth toxicosis (see Aspirin and Salicylate handout). Another form used medically is bismuth subnitrate; and with sufficient exposure the principle toxicologic concern is nitrate poisoning rather than bismuth overdose. Other trivalent, insoluble bismuth salts are also used orally for diarrhea and other gastrointestinal distress syndromes, and these rarely result in toxic consequences. The kidneys excrete bismuth and can concentrate it in the proximal tubules where it causes degeneration and necrosis. Inclusion bodies in the proximal tubules can be noted.

Nephrotoxic Organic Compounds

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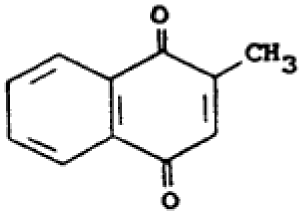
Vitamin K3

(Menadione)

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Nephrotoxic Organic Compounds
Horses	5 - 48 hours	5 - 7 days; often lethal	

Sources

- Vitamin K3 is synonymous with menadione N.F., Menaphthone®, Panosine®, and Synkay®. Vitamin K3 dimethyl pyrimidinol bisulfite is a related compound which is also called Hetrazene®. Vitamine K3 sodium bisulfite, also called menadione sodium bisulfite, Hykinone®, Klotogen®, Clotin®, and Vicasol® or just Vitamin K3®, is the actual form implicated in causing renal failure in horses. Menadione sodium diphosphate, USP, sometimes called Synkayvite® is also available.
- Whether forms of Vitamin K3 other than the sodium bisulfite salt are similarly toxic has not yet been determined and, for the present, they are all best avoided.
- Vitamin K4, also called menadione acetate, acetomenaphthone, Prokayvit®, and Kappaxin®, and vitamin K4 sodium diphosphate, also known as menadiol diphosphate tetrasodium salt or Synkayvit®, are also considered suspect because of their structural similarly to Vitamin K3.



Vitamin K3 (menadione)

Toxicity

- Initial recognition of an apparent toxic effect of vitamin K3 in the horse came about as a result of its empiric use to treat exercise-induced pulmonary hemorrhage or epistaxis in racehorses.
- Toxicosis may occur at the lowest recommended dosage of 2.2 mg /kg BW.
- The range of recommended dosages is from 2.2 - 11 mg/kg BW for the implicated vitamin K3 products.
- Dosage is recommended for these particular products by the intravenous and intramuscular routes. The influence of route of administration is not known, but one case of lethal renal failure occurred in a horse which was given a 3.75 mg/kg dose by the intramuscular route.
- The recommended total dose for man is only 2 - 10 mg.

Mechanism of Action

- Menadione sodium bisulfite causes hepatic and renal disease in rats. To date, in horses no hepatic lesions or dysfunction has been documented.
- In the rats, however, anemia, hemoglobinuria and urobilinogenuria also occurred.
- Similarly hemolytic anemia and kernicterus (severe jaundice and brain damage) in premature human infants has been observed following injection of large doses of menadione.
- Vitamine E-deficiency has been suggested as possibly playing a role in vitamin K3 toxicosis. In vitamin E-deficient premature infants or animals, auto-oxidation of vitamin K analogues may occur. It is

postulated that auto-oxidation may (despite normal glutathione concentrations) result in membrane instability in the red blood cell with hemolysis which may result in hemoglobin-induced nephrosis. This theory must be tested further before it can be accepted or rejected.

- Hemolytic anemia has not been observed in the equine patient although there is evidence of hemolysis and hemoglobinuria. At this time, it appears that hemolysis is not the primary nephrotoxic mechanism in equine nephropathy.
- The effect of vitamin K_3 in the horse is rapid with experimental horses exhibiting evidence of renal colic and hematuria within 4 - 12 hours.

Signs and Clinical Findings

- Onset of signs occurred in experimentally and otherwise dosed horses within 5 - 48 hours of injection of vitamin K_3 in most horses.
- Depression was the first clinical sign noted in closely observed horses.
- Signs of colic: slightly arched stance, rubbing of perineum and tail head on the stall, looking at the flanks, lying down and getting up, and stranguria were frequently observed.
- Some horses were mistakenly believed to be experiencing intestinal colic, however, clinical pathologic information allowed recognition of the renal component.
- Moderate to greatly enlarged kidneys on palpation.
- Frank hematuria in some horses. Microscopic evidence of hematuria in most cases.
- Anorexia.
- Fever in some affected horses.
- Occasionally noted clinical signs include: hemolysis, hemorrhage, disseminated intravascular coagulation, vasculitis, laminitis, and dependent edema.
- Death may occur within a few days, horses may recover after a clinical course of 5 - 7 days or they may experience chronic renal failure in some cases.

Clinical Pathology

- Proteinuria.
- Hematuria.
- Fixed specific gravity values (1.009 - 1.013).
- Elevated blood urea nitrogen and creatinine which correlate with the severity of the syndrome in individual animals.
- Serum electrolyte values were consistent with renal tubular disease in horses and included: hyponatremia, hypochloremia and hyperkalemia and less often hypercalcemia during the acute renal disease.

Lesions

- Gross enlargement and paleness of the kidney, which bulges from the cut surface.
- Histologically diffuse or multifocal tubular necrosis and dilation.
- Proteinaceous and cellular debris from red blood cells and neutrophils and casts were present in renal tubules.
- In surviving animals renal tubules still exhibiting degeneration, necrosis and dilation may be present in scattered areas of the kidney at 3 months after dosing. In chronic renal failure following vitamin K_3 administration, the kidneys may be greatly reduced in size, the capsule adherent, and pale streaks of connective tissue may be grossly apparent. On microscopic examination, the connective tissue appears massive, and the glomeruli hypercellular, and/or sclerotic. The tubules are dilated but the lining epithelium appear normal. Mineral, cellular, and proteinaceous casts may be seen in many tubules. Chronic mononuclear cell infiltrates are commonly observed.

Treatment

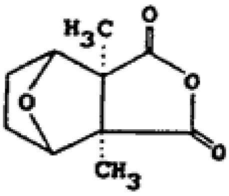
- No specific treatment has been investigated. It is most important to avoid using vitamin K_3 or vitamin K_4 in the horse in the first place.
- Fluids, bicarbonate (to reduce hemoglobin deposition in renal tubules) and good supportive care are indicated.

Blister Beetle - Cantharidin Toxicosis

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Horses, cattle, sheep	Hours	Few days; often lethal	

Sources

- Blister beetle = *Epicauta* spp. Includes "striped blister beetle", black blister beetle, others. Aid to identification is that the prothorax or "neck" is narrower than the head.
- Blister beetles, as adults, are usually leaf or flower feeders.
- Another blister beetle species, *pyrota insulata* has been found to cause cantharidin toxicosis when ingested by emu chicks in Texas.
- Toxicosis is due to ingestion of blister beetle itself.
- Problems occur primarily when beetles are present in alfalfa hay-southwestern U.S., plains states, occasionally in Illinois, Midwest, East.
- Increased incidence due to simultaneous cutting and crimping hay.
    - Separate cutting (traditional process) allows beetles to leave or settle out.
    - Found in alfalfa that is harvested at flowering.
- Over 100 beetles have been taken from 1 flake of hay.
- Spanish fly = cantharidins.



Cantharidin

Toxicity

- Cantharidin, bicyclic terpenoid, contained in the hemolymph, genitalia, and other tissues of beetle.
- Experimental feeding of crystalline cantharidin, at 489 - 720 µg/kg to horses, resulted in clinical signs of cantharidiasis and deaths.
- Toxicity of beetles varies, 4 - 6 grams air-dried ground beetles may be fatal.
- In some studies 30 beetles were lethal for a horse.

Mechanism of Action

- Unsure, strong mucosal irritant, causes hypocalcemia by an uncertain mechanism.
- Ingested cantharidin causes irritation of oral and GI mucosa leading to colic.

Susceptible Species

- Horses, cattle, rabbits, goats, and sheep reportedly poisoned by oral ingestion of beetles.
- Primarily horses, less often cattle.
- Morbidity ranges from sporadic to 100%.
- Other species including mice, rats, and dogs have been experimentally poisoned with ingestion of ground beetles or cantharadin.

Signs

- Variable, depends on dosage.

- Massive exposure can cause severe shock and death within hours-lethally affected animals die within 3 days.
- Mucous membrane irritant-severe oral, GI, and urinary tract inflammation and ulceration.
- Animals urinate frequently, rub perineum, exhibit prolonged episodes of repeated tenesmus.
- Colic, variable effects on intestinal motility.
- Hypocalcemia-synchronous diaphragmatic flutter = contraction of diaphragm with each heart beat (some persons may call this effect "thumps"). Hypocalcemia may be related to myocardial damage and/or shock.
- Listlessness.
- Rapid thready pulse (HR).
- Hemoconcentration with low urine specific gravity.
- Cyanosis, muddy mucous membranes.
- Rapid, shallow respiration, acidosis is not usually a feature.
- Shock and death.

Clinical Pathology

- Many observed changes in blood chemical parameters parallel those seen with colic, monensin toxicosis, and endotoxic shock.
- However, reduced total plasma calcium and magnesium concentrations in cantharidiasis help to differentiate this syndrome from other colic-like diseases and monensin toxicosis. Hypocalcemia and hypomagnesemia may last 1 - 2 days.
- Elevated BUN (variable).
- Leukocytosis.
- Hemoconcentration.
- Low urine specific gravity for the first day in spite of the hemoconcentration.

Lesions

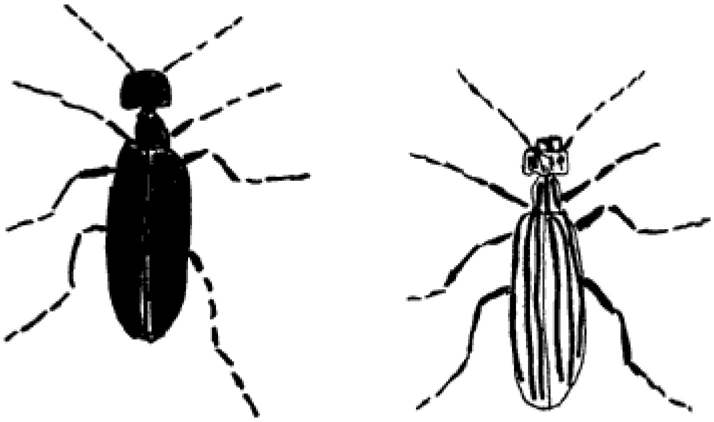
- Confined to GI, urinary tract and heart.
- Blistering, ulceration of mucous membranes of urinary bladder. Oral, esophageal, and gastric hyperemia or ulceration and enterocolitis occur.
- Myocardial streaking, necrosis, and degeneration.
- Renal damage.

Diagnosis

- Clinical signs, lesions pre- and postmortem.
- Identification of beetle in hay.
- Recently developed (GC-MS) technique for identification of cantharidin in the urine, GI contents.
- Low serum calcium and magnesium.

Treatment

- No specific antidote.
- Remove animals from suspect feed.
- Activated charcoal + saline cathartic.
- Fluid therapy in large volumes for shock, adjust for cardiac signs.
- Bicarbonate (notable losses may occur due to salivation and shock).
- Calcium gluconate and magnesium sulfate according to need.
- Parenterally administered antibiotics may be indicated for ulcerative mucosal damage.



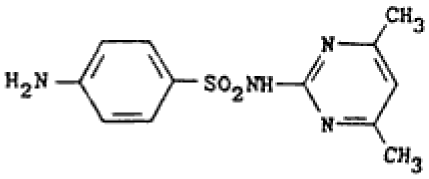
Black Blister Beetle and Striped Blister Beetle

Sulfonamides

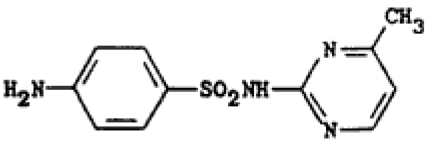
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Most species, esp. carnivores, poultry	Days to weeks	Days to permanent damage; potentially lethal	

Sources

- Sulfonamides are bacteriostatic, white powders which are sparingly soluble in water but very soluble in alkaline and strong acid solutions. Sulfonamides are used in the therapy of bacterial infections or prophylactically in livestock rations.
- Also found in some anticoagulant rodenticide formulations to potentiate vitamin K_1 inhibition.



Sulfamethazine



Sulfamerazine

Mechanisms of Action

- Antibacterial mechanism:
  - Sulfonamides are structural analogs of para-aminobenzoic acid (PABA) and competitively inhibit bacterial folic acid synthesis which utilizes PABA.
- Sulfonomides cause crystalluria leading to nephrotoxicity.
  - Sulfonamides are less soluble in an acid urine than in alkaline urine, therefore, crystal formation is generally greater in the urine of carnivores as compared to herbivores.
  - Dosage and duration of therapy are obvious considerations, since increased concentration increases the probability of crystallization in the urine. Toxicoses often result when the traditional dosage of 70 - 100 mg/lb of body weight is exceeded.
  - Administration of sulfonamides for longer than the customary course of 3 - 5 days may also increase the likelihood of poisoning.
  - Dehydration due to decreased water intake or diarrhea for any reason increases the probability of toxicosis.

- Other mechanisms of toxicity:
    - Sulfonamides may sometimes interfere with iodine metabolism and therefore be goitrogenic.
    - Sulfonamides may cause agranulocytosis and thrombocytopenia.
    - Sulfonamides may have the potential to cause methemoglobin formation.
    - Sulfonamides may inhibit carbonic anhydrase and therefore can cause diuresis and acidosis.
    - Sulfonamides may cause arrested fetal development.
    - Sulfonamides may cause a peripheral neuritis in chickens, and cattle.
    - Sulfonamides may cause an acute drug shock. The mechanism responsible for this effect is unknown.
    - Sulfas may also cause acute anaphylactoid reactions, apparently due to a hypersensitivity (immune mediated) reaction.
    - Topical applications of sulfonamides may inhibit wound healing.
    - Sulfonamides may possibly interfere with ruminal flora B-vitamin production or enteric vitamin-K synthesis, although little data exists for the theories.
    - Some sulfonamides, such as sulfaquinoxaline may directly antagonize the action of vitamin K in the liver. Poultry and especially dogs may develop changes in clotting function. Dogs may exhibit increased one stage prothrombin time and increased activated partial thromboplastin time, and clotting time.
    - Because they are highly protein bound to plasma proteins, it may be possible for sulfonamides to displace anticoagulant rodenticides from albumin, making them more available to hepatocytes and hence more toxic.
    - Sulfamethazine has been implicated recently as a tumorigen by virtue of the occurrence of thyroid enlargements in laboratory animal studies. This and the presence of residues in the tissue of animals no longer being given these drugs in their feed intentionally has caused great consternation among regulatory agencies and may result in cessation of the use of this drug as a feed additive on many farms.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorption-variable with type of sulfonamide administered. Some sulfas are rapidly absorbed from the GI tract, while others are poorly absorbed, "gut active" sulfas.
- Sulfonamides are metabolized to varying degrees, usually to conjugated or acetylated forms. Except for the pyrimidine sulfonamides, which include sulfamethazine, sulfamerazine and sulfadiazine, the acetylated forms readily pass through biological membranes, but are less soluble in the urine than the parent compounds.
- The different sulfonamides vary in toxicity in part as a result of their metabolism in the body. Sulfathiazole, for example, is highly excreted as the acetylated form and it is therefore more prone to cause toxicosis than most other sulfas.
- Sulfonamides undergo biliary and urinary excretion. They may also diffuse directly into the intestinal contents and undergo fecal excretion.
- Sulfonamides are excreted in the milk.
- Intrauterine use results in detectable blood levels in cattle for at least 48 hours.
- For more information of particular compounds, see page 1089 of Veterinary Pharmacology and Therapeutics, 5th edition, Booth and McDonald, eds.; and pages 716 - 717 of the same book.

Clinical Syndromes

- Toxicoses are most frequent in dogs, cats, poultry and baby calves.
- Five types of syndromes are most likely to occur:
    1. Chronic or renal form.
    2. Acute drug shock, which may be allergic but the actual cause is not known.
    3. Hypersensitivity (anaphylactoid).
    4. Photosensitivity.
    5. Acute toxicosis.

1. Chronic or Renal Form.
    a. **Most important and common form of toxicosis** associated with sulfonamides.
    b. Signs may include:
        - Anorexia

    - Depression, collapse
    - Hematuria, albuminuria, and oliguria. Sulfonamide crystals may be present on preputial or vulvar hairs.

  c. **Additional signs in cattle** may include:
    - Transient agranulocytosis.
    - Mild hemolytic anemia.
    - Leukopenia.
    - Reduced milk production.
    - Spinal and peripheral neuropathy.

  d. **Additional signs in dogs** may be related to coagulopathy, although the greatest concern is when the sulfonamide is formulated with an anticoagulant rodenticide such as warfarin in order to potentiate its inhibition of vitamin K function. Keratoconjunctivitis sicca commonly occurs. Hepatopathy may develop.
  e. **Additional signs in poultry** may include:
    - Poor egg production
    - Spinal and peripheral neuropathy
    - Poor growth

2. Acute "drug shock".
  a. **In calves** results from rapid IV administration.
    - Mydriasis
    - Ataxia
    - Blindness
    - Collapse
    - Possible death

  b. **In dogs** may occur after large parenteral or oral doses.
    - Emesis
    - Ataxia
    - Spastic paralysis
    - Epileptiform convulsions
    - Diarrhea

3. Hypersensitivity.
  a. Anaphylactoid reactions.
    - Occurs in **horses** and **cattle**.
    - Manifested as asthma or urticaria (hives).
    - Cross-reactions between sulfonamides may occur with animals reacting similarly to more than one member of the group.

  b. Drug allergy from trimethoprin-sulfadiazine.
    - Hypersensitivity reactions observed in Doberman Pinscher dogs. Clinical signs mimic immune-mediated disorder and include nonseptic polyarthritis, fever, polymyositis, anemia, and lymphadenopathy. Glomerulonephropathy, focal retinitis, leukopenia, and thrombocytopenia were also observed.
    - Reactions developed 10 - 21 days after the first drug exposure and/or within 1 hour to 10 days after reexposure.

4. Photosensitivity.
  - Sulfonamides infrequently cause photosensitivity. Skin rashes may result and these may be seen inconjunction with other effects such as hemolytic anemia and agranulocytosis.

5. Acute toxicosis.
  - Acute toxicosis from high doses of sulfonamides is **rare**.
  - Hypersalivation, vomiting, diarrhea.
  - Increased respiratory rate.
  - Weakness, ataxia, and spastic rigidity.

Lesions

- Few gross changes except for the presence in some animals of sulfonamide crystals in the renal pelvis and renal tubules. Kidneys may be gritty in texture when cut.
- Specimens of kidney tissue should be fixed in a slightly acidified formalin solution or in absolute ethanol to prevent dissolution of the crystals, which are readily observed microscopically in stained slides, especially with polarized light.
- Bone marrow depression may sometimes be seen.
- Hemorrhagic diathesis may be seen in birds receiving sulfaquinoxaline.
- In photosensitivity, appropriate skin lesions may be seen.
- Secondary effects of uremia may be noted in the renal form.

Diagnosis

- Appropriate history of exposure and lesions are very important in the diagnosis.
- Chemical confirmation is important in many cases and appropriate specimens, depending upon the likely source, may include:
    - Feed
    - Premix
    - Water
    - **Note**: With some methods of analysis, arsanilic acid and procaine penicillin may give false-positives.
- Concentrations of a sulfonamide in muscle, kidney, or liver above 20 ppm substantiate a diagnosis.
- In hypersensitivity, a history of previous exposure to sulfonamides and appropriate clinical signs warrants a tentative diagnosis.
- In anaphylactoid reactions, very recent initial exposure and appropriate clinical signs warrant a tentative diagnosis.

Treatments

- Terminate exposure. In the rare case of acute overdose, judicious efforts should be undertaken to evacuate the gastrointestinal tract, using an emetic, lavage, saline cathartic, and/or adsorbent as indicated by the dosage, time factors, and species involved.
- Obviously removal of sources in the feed and water must also be accomplished.
- The half-life of sulfonamides can be decreased by the administration of fluids and by increasing the urine pH. Fluid therapy may therefore be indicated and alkalinization of the urine is recommended using bicarbonate either in the fluids or orally. Fluid therapy must be monitored to prevent overhydration in anuric animals.
- Vitamin K_1 is indicated in cases of hypoprothrombinemia or concurrent exposure to a coumarin or indandione anticoagulant.
- Acute anaphylactoid reactions may be treated with epinephrine.
- Hypersensitivity reactions may be treated with antihistamines if needed.
- When possible, other drugs which are protein bound should not be used in animals already carrying toxic concentrations of sulfonamides on board since the sulfas may be displaced from the albumin, diffuse into tissues or be filtered by the kidney resulting in increased toxic effects.

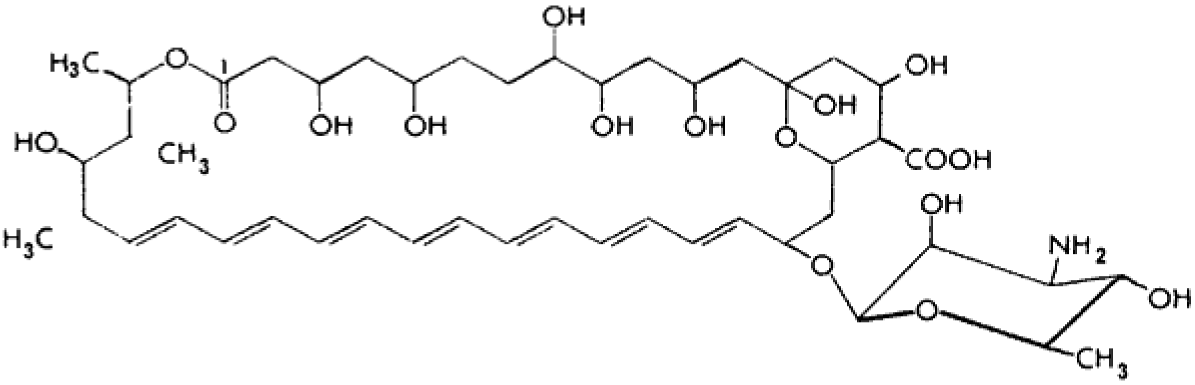
Amphotericin-B

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Most species	Days to weeks	Few days to permanent damage; potentially lethal	

Sources

- Amphotericin-B (Fungizone) is a polyene antibiotic used in the treatment of various systemic mycotic infections such as:

  - Coccidioidomycosis.
  - Histoplasmosis.
  - Candidiasis.
  - Blastomycosis.
  - Aspergillosis.
- The drug is prepared for IV injection.



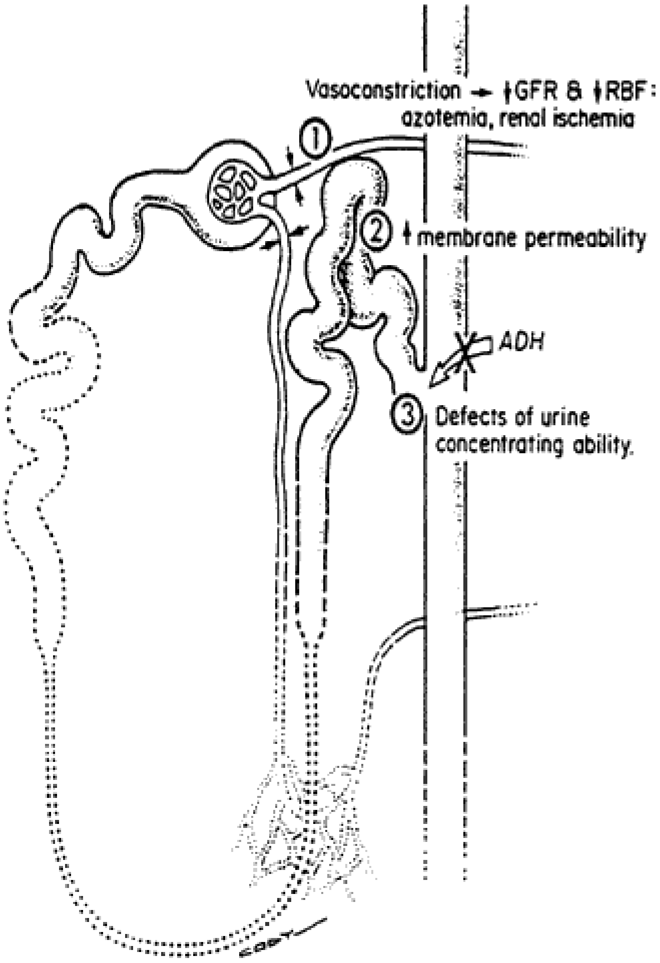
Amphotericin B

Toxicity

- Amphotericin-B is nephrotoxic at recommended dosage rates and renal toxicity is expected in most courses of therapy at some point.
- Reversible renal dysfunction develops in more than 80% of human patients receiving amphotericin-B. The same renal dysfunction routinely occurs in veterinary patients as well.
- For this reason, the drug is often used every other day or in courses of one week on, one week off, etc.
- Generally, the blood urea nitrogen is monitored before and during the course of therapy and treatment is continued as long as the BUN remains below 40 mg%.
- Such infections are often treated for 6 - 8 weeks.

Mechanism of Action

- Poor oral absorption, therefore given intravenously. Persists in blood for 18 - 24 hours at comparatively high concentrations.
- Amphotericin-B interacts with sterols of cell membranes forming pores or channels which leak various small molecules (see mention of chloride below), thereby disrupting cellular compartmentalization of the cell from the outside (intercellular) environment.
- Most of the adverse effects of amphotericin are probably related to disruption of the mammalian cell membrane.
- Nephrotoxicity may be related to a decrease in intrarenal blood flow associated with arteriolar vasoconstriction, a subsequent decrease in GFR, and impaired tubular function.
- Nephrotoxicity may be explained further on the basis of a tubuloglomerular feedback mechanism. Amphotericin causes an increase in permeability to chloride ions, causing excess chloride to be presented to the distal tubule. A tubuloglomerular feedback response causes a compensatory decrease in GFR and renal blood flow to occur. Excessive response has the potential to cause ischemia.
- Amphotericin-B has also been reported, in man and rats, to cause renal tubular acidosis.
- Defects of urine concentrating ability occurs in dogs and man. May reduce response to antidiuretic hormone (ADH).
- Low erythropoietin production during therapy may result in anemia.



Pathophysiology associated with amphotericin B nephrotoxicity - Amphotericin acts on several sites of the nephron. At site 1 there is vasoconstriction, either as the result of direct action of the drug on the vessels or by reflex mechanisms. This results in decreased renal blood flow and azotemia; it may increase renal damage by causing renal ischemia. At site 2 the membranes of the distal tubule cells show altered permeability. This may initiate reflex mechanisms to decrease GFR (by tubuloglomerular feedback) and may cause excessive loss of electrolytes, producing hypokalemia and distal renal tubular acidosis. At site 3 the action of ADH is antagonized, which produces defects in urine concentration*. (Figure from Current Veterinary Therapy IX, Small Animal Practice)*

Signs

- Fever.
- Nausea, vomiting, and diarrhea.
- Anorexia and weight loss.
- Polyuria, oliguria, or anuria.
- Increased numbers of casts in the urine sediment (granular or cellular).
- Hematuria or proteinuria.
- Anemia.

Treatment

- Maintaining good hydration is essential in prevention of clinical toxicosis in the first place.
- Therapy is largely directed at supporting renal function and assisting detoxification of nitrogenous byproducts as in other forms of kidney failure.
- Fluids are indicated and the concomitant use of mannitol with amphotericin-B has been found to reduce its nephrotoxicity in dogs. Sodium loading decreases amphotericin toxicity.
- Monitor PCV, total protein, BUN, and serum creatinine. Therapy should be discontinued if BUN becomes abnormal or if severe systemic toxic signs appear such as depression or vomiting.
- If hypokalemia develops, potassium supplementation should be instituted.

Other Nephrotoxic Antibacterial Agents

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Most species	Days to weeks	Days to permanent damage; potentially lethal	

Introduction

The kidney is exceptionally vulnerable to toxicants. Renal blood flow accounts for 20% of cardiac output, with 90% of this going to the renal cortex. The kidney also consumes oxygen at an extraordinary rate, making it quite sensitive to cellular hypoxia. The countercurrent mechanism of the kidney also predisposes the medullary interstitium to toxicity because of the progressively increasing tissue concentrations of nephrotoxic agents.

Sources

- Antibacterials: aminoglycosides, cephalosporins, isoniazid, penicillins, sulfonamides (see separate section), tetracyclines.
- Antifungals: amphotericin-B.
- Anthelmintics: arsenicals, thiacetarsamide.
- Analgesics: NSAID, acetaminophen, ibuprofen, phenylbutazone, salicylates.
- Bacitracin:
    - Strongly nephrotoxic when given parenterally, therefore not given by this route. Not absorbed orally, so can be used for gastrointestinal infections. Also widely used topically.
- Polymyxin-B:
    - Not absorbed from the skin or intestine but sometimes used by injection.
    - Occasional toxicosis, primarily affecting renal and otic function results from parenteral administration. Dogs are especially sensitive.
- Tetracyclines:
    - The use of tetracyclines can result in progressive azotemia due to antianabolic effects of these drugs. Uremia is more pronounced in animals with preexisting renal disease.
- Oxytetracycline:
    - One report in calves.
- Cephalosporins:
    - Cephaloridine is the most nephrotoxic of all available cephalosporins.
    - Occasionally reported as a cause of acute renal failure in dogs and cats.
    - Inhibits renal cation transport, which may lead to an increase in drug concentration within the renal cortex.
    - Cephaloridine depletes cortical glutathione which leads to membrane lipid peroxidation and necrosis.
- Penicillins:
    - Not directly nephrotoxic. Nephrotoxicity dependent upon immune-mediated hypersensitivity.
- Aminoglycoside antibiotics:
    - Aminoglycosides have a low therapeutic index and renal dysfunction may occur in 10 - 20% of all courses of therapy.
    - Aminoglycosides include gentamicin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin.
    - All aminoglycosides are nephrotoxic and ototoxic. Each has an ability to damage renal proximal tubules. neomycin is considered the most neophrotoxic aminoglycoside. The other nephrotoxic aminoglycosides in decreasing order of toxic potential are: gentamicin, tobramycin, amikacin, and streptomycin.
    - Mechanisms.
        - Aminoglycosides are eliminated by glomerular filtration. Proximal tubules of the kidney actively uptake aminoglycosides. Continued use increases the likelihood of nephrotoxicity.
        - Risk factors that predispose a patient to nephrotoxicity include prolonged therapy, preexisting renal disease, advanced age, dehydration, concomittant exposure to other nephrotoxic agents, and diuretic (especially furosimide) use.

        - Exact cellular mechanisms of nephrotoxicity are unknown but may include inhibition of protein synthesis, inhibition of phospholipases, altered mitochondrial action, and inhibition of Na-K ATPase function.
- Neomycin:
    - Poorly absorbed after oral or topical administration.
- Gentamicin:
    - Widely used for systemic bacterial infections and for urinary infections in spite of its nephrotoxic properties. Renal function should be closely monitored in vigorously treated patients and in all patients on extended courses of therapy. In the presence of renal disease or urinary obstruction, other drugs should be selected whenever possible.
    - Clinical signs of nephrotoxicity are referable to acute tubular necrosis and acute renal failure.
    - Gentamicin nephrotoxicity follows 4 stages including: **1**) functional changes (polyuria, proteinuria, glucosuria), **2**) proximal renal tubular cell death (casts), **3**) decreased GFR (azotemia), and **4**) regeneration when cell necrosis is complete.
    - Treatment-Nephrotoxicosis due to aminoglycosides is usually reversible. Discontinue use of the offending drug. Avoid the use of loop diuretics. Institute fluid therapy (and hemodialysis if necessary) as for other causes of acute renal failure.

Carbamate Fungicides

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
-	-	-	

Sources

Carbamate fungicides such as Maneb and Zineb are widely used in orchards and garden and agricultural applications.

Toxicity

- Very low in toxicity. Rat oral median lethal doses:
    - Zineb LD_{50} was > 5,200 mg/kg.
    - Maneb LD_{50} was 7,990 mg/kg.

Effects

Nephrotoxic and hepatotoxic but only at massive exposure rates.

Comments

The primary reason to mention these compounds is that it is important to avoid confusion of these compounds with the carbamate insecticides, some of which are extremely toxic inhibitors of acetylcholinesterase.

Analgesic Nephropathy

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Non-steroidal anti-inflammatory drugs See Nonsteroidal Anti-Inflammatory Agents	Small animals, horses	Hours to days	Days to permanent damage; often lethal	

Note - See also Nonsteroidal Anti-Inflammatory Agents.

I. Introduction

Analgesic nephropathy was first described in 1953 in human patients as the result of prolonged consumption of combination analgesics containing phenacetin, aminopyrine, caffeine, isopropylantipherine, and persedon [1]. Since that time, the development of papillary necrosis has become recognized as a characteristic pathologic finding in the classic syndrome [1]. Clinically, analgesic nephropathy is characterized in humans by the development of: proteinuria, decreased glomerular filtration rate (GFR), hematuria, anemia, and flank pain. In addition to papillary necrosis, a number of renal syndromes have become associated with the consumption of nonsteroidal anti-inflammatory drugs in both animals and humans [2-4].

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a wide range of pharmacologically active agents with diverse chemical structures. Chemical classes of NSAIDs include: **a**) salicyclic acid derivatives (e.g., aspirin), **b**) phenylacetic acids (e.g., diclofenac), **c**) heterocyclic acetic acids (e.g., indomethacin, sulindac), **d**) proprionic acids (e.g., ibuprofen, naproxen), **e**) fenamic acids (e.g., flufenamic), **f**) pyrazolones (e.g., phenylbutazone), and **g**) oxicams (e.g., piroxicam). Among all NSAIDs, the common mechanism of action for their anti-inflammatory properties resides in their ability to inhibit cyclooxygenase, an enzyme required for prostaglandin synthesis.

II. Review of Prostaglandin Effects on the Kidney

A. Prostaglandin synthesis

Prostaglandins (PGs) are unsaturated fatty acids which are derived from 20-carbon essential fatty acids, of which the most important is arachidonic acid. Arachidonic acid is released from damaged cell membranes and is metabolized by either cyclooxygenase, which leads to PG formation, or lipoxygenases, which results in leukotriene synthesis.[5] The biological activity of most PGs is exerted primarily at the local site of synthesis due to their short circulatory half-life.

In the kidney, the major vasodilatory prostaglandins are PGE_2 and PGI_2 (prostacyclin), the production of which is stimulated by vasoconstrictive substances including angiotensin II, norepinephrine, and antidiuretic hormone. The major physiologic role for vasodilatory PGs is to modulate the pressor effects of vasoactive substances on the kidney and maintain adequate renal blood flow (RBF) and GFR. The modulating action of PGs plays a minimal role in controlling renal function in healthy euvolemic individuals, but during certain pathophysiologic states, vasodilatory PG production is required to maintain adequate renal perfusion and function.

Renal prostaglandin synthesis is compartmentalized; for example, microsomes isolated from cortical as well as medullary portions of the kidney are capable of producing PGD_2, PGE_2, PGF_2, PGI_2, and TxA_2 in varying amounts. In general, the bulk of PG synthetic capacity is located in the medulla [6]. The location of PG degradative enzymes within the kidney is not as well delineated (versus sites of biosynthesis). Considerable spontaneous hydrolysis is likely.

B. Physiologic actions of prostaglandins

1. **Renal blood flow** - Studies in the dog show that PGE_2, PGD_2, and PGI_2 reduce total renal resistance and increase renal blood flow, whereas PGF_2 and 6-keto PGF_1 (hydrolysis product of prostacyclin) exert little or no effect [7-9]. Prostaglandins also influence the intrarenal distribution of blood flow; for example, intrarenal infusion of arachidonic acid in the dog results in greater increases in inner cortical blood flow than in the outer [10]. Conversely, the NSAID indomethacin shifts cortical blood flow to superficial regions, decreases medullary blood flow, and reduces blood flow rate in papillary vasa recta capillaries.

   In the conscious dog or baboon, inhibition of PG synthesis has little or no effect on renal blood flow [11]. The experimental use of cyclooxygenase inhibitors provides supportive evidence for the role of PGs in attenuating the renal vasoconstrictive influences of angiotensin II, norepinephrine, and alpha-adrenergic neural stimulation. Although PGs modulate the effects of vasoconstrictors on the renal microcirculation, there is little evidence that these compounds play a role in autoregulation. For example, in intact dogs, autoregulation of RBF and GFR is well preserved despite pretreatment with indomethacin [12]

2. **Glomerular filtration** - Inhibition of PG synthesis does not impair GFR in normovolemic animals or man, but in states of high plasma concentrations of endogenous angiotensin II (e.g., low cardiac output, volume depletion, or dietary sodium restriction), blockade of PG synthesis causes a significant decline in GFR [10,13].
3. **Renin release** - Prostaglandins play an important role in mediating renal renin release. In intact animals, infusions of arachidonic acid, PGD_2, PGE_2, and PGI_2 all have been demonstrated to increase plasma renin activity [14,15]. In addition, blockade of PG synthesis with indomethacin decreases plasma renin activity in vivo both under normal resting conditions and when renin release is increased.
4. **Electrolyte excretion** - Renal electrolyte transport can be modified by PGs via several mechanisms. Prostaglandins counterbalance angiotensin II-induced vasoconstriction of the efferent arteriole, which increases GFR and decreases proximal tubular reabsorption. Proximal tubular reabsorption can also be influenced by changes in medullary tonicity. Prostaglandins increase blood flow to the inner cortex which increases flow through the efferent arterioles and the renal medulla. Sodium reabsorption and medullary tonicity decrease secondarily to these changes in hemodynamics. In addition, passive reabsorption of sodium is also decreased by the inhibitory effect of PGs on chloride reabsorption in the ascending loop of Henle. Prostaglandins may also directly inhibit sodium reabsorption by the distal nephron [16].

   Renal concentrating mechanisms are also susceptible to the effects of PGs. The formation of concentrated urine requires inner medullary hypertonicity and maximal water permeability of the collecting duct. In addition to their hemodynamic effects, PGs also reduce urea accumulation in the medullary interstitium. There is poor reabsorption of urea and a decrease in reabsorption of sodium which also alter medullary blood flow. Alteration of medullary blood flow results in decreased medullary interstitial osmolarity, which results in the production of a more dilute urine. Prostaglandins also affect water balance because of natriuretic effects and possibly by altering the PGE-controlled blockade of ADH-induced water reabsorption [16].

III. Clinical (Renal) Syndromes Associated with NSAIDs

Several types of acute renal dysfunction have been associated with the use of NSAIDs, the most common being: acute renal failure, hyperkalemia, and acute interstitial nephritis with or without proteinuria (Table 1). The most commonly encountered adverse renal effect related to the use of NSAIDs is prostaglandin-dependent renal insufficiency [3,17].

A. Acute renal failure

Prostaglandin-mediated acute renal failure is characterized by oliguria, azotemia, and occasionally hyperkalemia. In general, NSAID-mediated acute renal insufficiency is reversible, and discontinuation of NSAID therapy results in a return to basal renal function.

Phenylbutazone has been implicated in the horse in the development of acute renal failure; renal medullary crest necrosis; and oral, gastric, duodenal, and colonic ulcers [18,19]. In addition, uremia and gastrointestinal ulceration have also been described in dogs following the ingestion of ibuprofen [20] and naproxen [21]. Acute renal failure as a result of decreased production of vasodilatory prostaglandins (PGE_2 and PGI_2) most commonly occurs when systemic vasoconstrictive influences are present (Table 2). Water deprivation has been demonstrated to be a potential risk factor which predisposes horses to the development of phenylbutazone nephropathy [22]. The appearance of analgesic nephropathy and papillary necrosis are thought to be the result of an ischemic process and endothelial necrosis. The development of renal medullary ischemia is considered to be the initiating factor in the production of papillary necrosis. The apparent predisposition for the development of lesions at the papillary tip is believed to be the result of higher relative concentrations of drug and metabolites in this region of the kidney, as well as the relatively poor blood supply to the renal papilla when compared to the rest of the medulla. Experimental NSAID administration to anesthetized animals has revealed medullary ischemia as a result of shunting of blood flow from the renal medulla to the cortex [23].

In human patients, a syndrome of acute oligoanuric renal failure has also been associated with phenylbutazone use. One proposed mechanism for the development of "phenylbutazone anuria" in human patients is a phenylbutazone-mediated inhibition of uric acid reabsorption which results in hyperuricosururia, uric acid urolithiasis, and bilateral ureteral obstruction [24]. Irreversible renal injury in the form of papillary necrosis has also been associated with ibuprofen, fenoprofen, and mefenamic acid therapy in human patients.

B. **Hyperkalemia**
Prostaglandins mediate the release of renin in response to changes in blood pressure and sodium delivery to the macula densa. Prostaglandins may also stimulate aldosterone production through influences on renin release. Decreased renal prostaglandin synthesis as a consequence of NSAID use in humans has been implicated as a cause of hyporeninemic hypoaldosteronism [25]. The treatment of hyporeninemic hypoaldosteronism with furosemide (administration stimulates renal prostaglandin release) provides additional supportive evidence for the role of PGs in renin release. Decreased plasma renin activity has been reported in man for virtually all NSAIDs with the possible exception of sulindac. The persistence of hypoaldosteronism in the presence of marked hyperkalemia is further supportive evidence that potassium-mediated secretion of aldosterone by the adrenal cortex is also suppressed. In addition, hyperkalemia may be a result of a PG-induced defect in cellular uptake of potassium [11].

C. **Interstitial nephritis** [2,3]
There have been case reports involving human patients who developed a syndrome of acute renal failure with proteinuria following NSAID administration. Onset generally occurs from 2 weeks to 18 months after the initiation of NSAID therapy. Steroids have been used to accelerate recovery, although their efficacy remain unproven. Microscopic examination of the urine sediment frequently reveals evidence of hematuria and pyuria. The combination of an "active" urine sediment and proteinuria in the absence of prior renal compromise helps differentiate this syndrome from other forms of NSAID-related acute renal failure. Histologic examination demonstrates normal renal glomeruli, focal diffuse interstitial infiltrates consisting primarily of lymphocytes, and vacuolar degeneration of the proximal and distal tubules. In general, the glomeruli are minimally altered with extensive fusion of epithelial-foot processes occasionally noted.

This syndrome has been reported in human patients taking fenoprofen, naproxen, tolmetin, sulindac, and indomethacin. Despite its idiosyncratic nature, the syndrome is produced by at least 2 structurally distinct NSAID classes (phenylproprionic acid and indoacetic acid derivatives) which may represent a common metabolic pathway. It has been proposed that interstitial nephritis may be the result of T cell activation and secondary autoimmune-mediated damage. Inhibition of cyclooxygenase by NSAIDs may also lead to shunting of arachidonic acid precursors into the lipoxygenase pathway, which would favor production of lymphokine-like inflammation-inducing metabolites of eicosatetraenoic acid.

IV. Clinical Management

See Nonsteroidal Anti-Inflammatory Agents for important information on management of animals with NSAID overdose.

A. **Analgesic nephropathy**
In general, acute renal insufficiency resulting from prior NSAID administration has been considered reversible. Dopamine has sometimes been recommended for the treatment of human patients with NSAID-induced interstitial nephritis. In general, the development of papillary necrosis (as a result of NSAID use) is considered an irreversible condition. It should be noted, however, that renal papillary necrosis has been considered to be an incidental finding in some horses treated with phenylbutazone and may not necessarily result in compromised renal function [27]. The use of synthetic PGE_2 has been examined for possible benefits in the prevention of phenylbutazone toxicoses in ponies. The administration of synthetic PGE_2 (before and after the daily administration of phenylbutazone) in these animals resulted in a reduction in the formation of gastrointestinal ulceration and hypoproteinemia [28]. Prostaglandin E analogs, such as Misoprostil® are now recommended for animals with acute analgesic nephropathy.

B. **Acute NSAID overdose**
The most commonly encountered situation in small animal toxicology is the massive, acute ingestion of NSAID-containing medications. Management of acute NSAID poisoning is essentially symptomatic and supportive. In recent ingestions, the oral administration of single or repeated doses of activated charcoal will reduce the absorption of most NSAIDs [29]. The use of dopamine and/or dobutamine may increase renal perfusion and minimize the degree of renal insufficiency. Occasionally, animals may develop seizures following the ingestion of large quantities of NSAID, and the use of diazepam to abolish seizure activity is indicated. The most prevalent adverse side effect encountered as a result of NSAID ingestion is the development of gastrointestinal irritation and ulceration. The use of sucralfate and cimetidine has been recommended for the treatment of NSAID-induced gastric ulceration.

V. Conclusions

Analgesic nephropathy is primarily an extension of the pharmacologic action of these agents (inhibition of prostaglandin production by the kidney). In the kidney, PGE_2 and PGI_2 primarily function as vasodilatory agents, and during certain disease states (e.g., congestive heart failure, water depletion), the production is required for compensatory renal autoregulatory mechanisms. Historically, it has been during these disease states that analgesic nephropathy most commonly occurs. The inhibition of prostaglandin synthesis by NSAIDs can also predispose some individuals to the development of interstitial nephritis, electrolyte imbalances (e.g., hyperkalemia), and water retention. Areas of apparent ongoing research efforts and controversy include:

A. The localization and extent of prostaglandin synthesis within the kidney. In addition, characterization of the types, amounts, and physiologic activity of prostaglandins produced by renal tissues. Future effort into the delineation of the compartmentalization of prostaglandin degradative enzymes within the kidney is also needed. Research efforts into these areas have been hampered by the use of *in vitro* tissue culture techniques which minimize renal blood and tubule fluid dynamics and the lack of sensitive chemical assays for the presence or absence of prostaglandins and associated enzymes.
B. Determination of the correlations between observed renal toxicity and the urinary excretion of prostaglandins. Measurements of urinary prostaglandins and correlation to renal cyclooxygenase activity have been hampered because of the concurrent production of potentially cross-reacting metabolites, namely some of the prostaglandins and thromboxane.
C. Studies into the prevalence of and risk factors for the development of analgesic nephropathy and NSAID-induced renal insufficiency in companion animals are needed. As the population of geriatric animals increases, a growing number of animals are likely to receive NSAIDs. In addition, characterization of the renal syndrome(s) produced by chronic use of NSAIDs in companion animals is needed. Of additional concern is the need to identify likely threshold doses for the development of renal insufficiency in acute NSAID overdose in companion animals.
D. Further studies into the pathophysiologic mechanisms which underlie the development of papillary necrosis, interstitial nephritis (e.g., the role of humoral response), and electrolyte imbalance is also needed. Similarly, studies into potential therapeutic regimens for the treatment of analgesic nephropathy are needed (e.g., the efficacy of steroids in interstitial nephritis, potential use of synthetic prostaglandins in preventing or modifying toxicity).

Table 1 - Clinical syndromes of nephrotoxicity with NSAIDs.
1. Renal insufficiency: Prostaglandin synthesis of nephrotoxicity with NSAID-enhanced renal vasoconstriction often in the context of diminished basal renal blood flow.
2. Hyperkalemia: Prostaglandin synthesis inhibition leads to hyporeninemic hypoaldosteronism and resultant hyperkalemia.
3. Interstitial nephritis: Direct nephrotoxicity, often results in heavy proteinuria.
4. Sodium and water retention: Diuretic resistance possibly due to aldosterone-like effect of NSAIDs as well as antinatiuretic effect of PG synthesis inhibition; water retention in part secondary to PG synthesis inhibition and enhanced effect of vasopressin.
5. Anaphylaxis

Table 2 - Clinical and experimental conditions in which renal function is prostaglandin dependent.
1. Low renal perfusion pressure by hemorrhagic hypotension.
2. Extracellular volume depletion of diuretics.
3. Anesthesia and surgical stress.
4. Reduced cardiac output.
5. Renal disease including nephrotic syndrome or chronic glomerulonephritis.
6. Hepatic cirrhosis (ascites).

7. Arteriosclerotic cardiovascular disease (human patients).

Other Agents Causing Nephrotoxicoses and Oxalate Excretion

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Ethylene glycol	(See Toxicants that Cause Acidosis)			
Oxalic acid (rust remover)	Mostly dogs	Minutes to hours	Few days to permanent damage; often lethal but toxicosis is rare	

Ethylene Glycol -

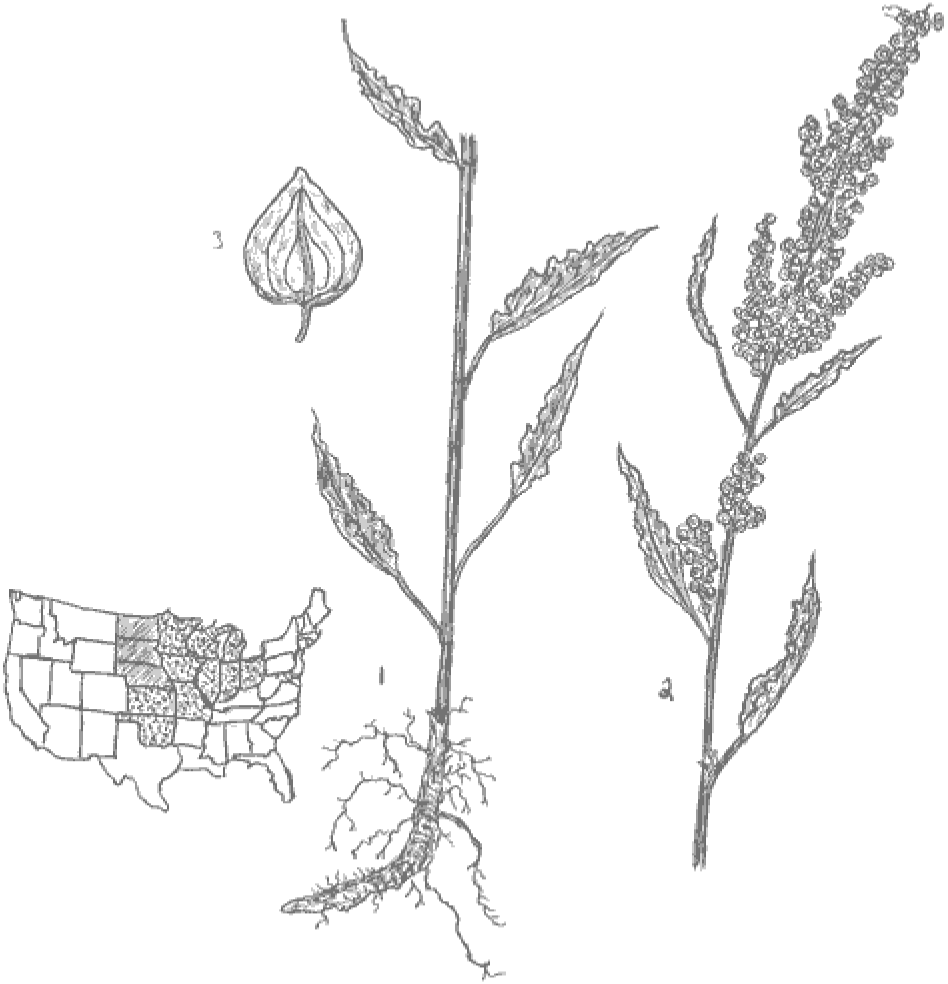
As mentioned under agents causing acidosis, ethylene glycol toxicosis causes a nephrosis characterized by dilated tubules with damage to tubular epithelial cells, deposition of calcium oxalate crystals, and both oxalate and hippurate crystaluria. Renal failure may result in an acute illness after the animal has survived the acidosis stage or, after repeated ingestions, may be the principle problem first encountered. Usually, if the animal survives an acute toxicosis, the renal effects of ethylene glycol resolve with time; however, in some cases chronic renal failure results.

Oxalic Acid -

Oxalic acid is available in crystalline form over-the-counter and people use it for rust removal from various surfaces and from fabrics. Although rarely encountered by domestic animals, this can be a potent toxicant causing serious or lethal toxicosis. Anticipated effects include gastrointestinal irritation, oxalate crystalluria and oxalate nephrosis and possibly acute hypocalcemia and death.

Rumex -

A genus of oxalate containing plants not mentioned in the subsequent section of these notes is *Rumex* spp., also known as curly dock, sour dock, or sheep sorrel.



Curly Dock, *Rumex crispus* L. **1**, lower part of plant; **2**, upper part of plant; **3**, seed; **4**, distribution. **Perennial**, with large, yellow, somewhat branched taproot, reproducing by seed. **Stems** smooth, erect, 1 to 4 feet (0.3 to 1.2 m) tall, single or in groups from the root crown.

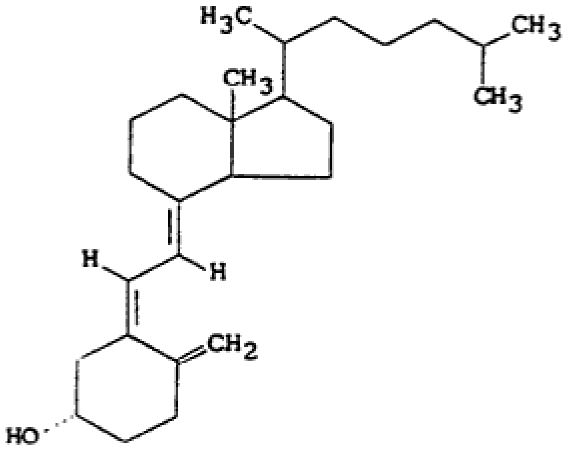
Cholecalciferol-Based Rodenticides and Other Vitamin D-Containing Products. Multiple Vitamin Preparations

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Vitamin D3 (especially cholecalciferol rodenticides)	Dogs, other pet animals	24 - 72 hours	Weeks to permanent damage; often lethal	

Sources

- Cholecalciferol (Vitamin D$_3$)-containing rodenticides are marketed as, among others, Quintox® (Bell Laboratories), Rampage, Ortho Rat-B-Gone, and Ortho Mouse-B-Gone® brand names. Marketed as an acute single feeding or chronic (multiple feeding) rodenticide.
- Quintox® is available in 2 bait forms: a mouse seed (sold as 10 gram place pac) and a cereal rat and mouse bait (sold as 30 gram pouch). The Ortho products are available in a box that contains four 40-gram packs.
- Muritan® is also listed as a rodenticide source of cholecalciferol in the book, Farm Chemicals '96.
- Cholecalciferol is present at 0.075% concentration in final bait formulations. Cholecalciferol naturally exists in animals as a precursor of active vitamin D. Its intrinsic biological activity, however, is low.
- Advertised as having no bait shyness, and reported effective against anticoagulant-resistant rodents. Rodent deaths delayed 2 - 5 days. After lethal dose is consumed all feeding stops.

- Cod liver oil is another source of Vitamin D as well as Vitamin A.
- See also Vitamin D containing plants (next section).
- Vitamin D_2 (ergocalciferol) is the plant form of Vitamin D. It is not utilized by poultry and only poorly utilized by swine.)
- Calcipotriene (Dovonex® ointment and less often lotion) used for humans with psoriasis has repeatedly poisoned dogs.



Vitamin D_3
Cholecalciferol

Toxicity

- Based upon clinical reports, toxicoses have occurred in dogs from the ingestion of cholecalciferol at 0.5 - 3 mg/kg body weight. Administration of 10 - 20 mg/kg to dogs of cholecalciferol-based rodenticide resulted in death in 4 dogs.
- Younger animals appear at higher risk to the development of toxicosis.
- Acute oral LD_{50} in dogs of technical material in oil has been reported to be 85 mg/kg. This has lead to an **underestimate of the actual hazard** of the rodenticide products for this species.
- Relay toxicosis: not reported in experimental studies.
- 40 IU vitamin D = 1 mcg. Thus, 1 IU of vitamin D_3 = 0.025 mcg of cholecalciferol.

Mechanism of Action

- Calcium homeostasis is under the control of: **1**) parathyroid hormone (PTH), **2**) calcitonin, and **3**) vitamin D metabolites. Calcium concentration of the blood is composed of "diffusible calcium" including the citrate bound and free calcium ion (ionic calcium) fraction (40%), and a "nondiffusible" protein-bound fraction (30 - 50%).
    - Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid gland. Parathyroid hormone feedback system is relatively simple, controlled primarily by serum calcium ion concentration (magnesium ion has lesser effects). As serum calcium levels rise, PTH levels decline. Parathyroid hormone has its primary effects on the bone, kidney, and to a lesser degree the intestine. PTH acts on bone to mobilize calcium (from skeletal reserves) into the extracellular fluid (increased osteoclasic and osteocytic activity. Prolonged PTH levels results in increased osteoclast numbers). PTH exerts a rapid effect on the proximal renal tubules resulting in decreased phosphate reabsorption. PTH also enhances distal convoluted tubule reabsorption of calcium. Finally, increased intestinal absorption of calcium occurs as a result of PTH influence.
    - Calcitonin (CT) is secreted by thyroid parafollicular (C) cells. PTH and CT have antagonistic effects on bone reabsorption, but synergistic effects on renal tubular reabsorption of phosphorous. Blockade of osteoclastic and osteocytic bone reabsorption occurs as a result of calcitonin activity.
    - Cholecalciferol (vitamin D3) is synthesized in the epidermis under the influence of sunlight from its precursor, 7-dehydrocholesterol. Vitamin D binding protein transports cholecalciferol from the skin into the blood. Vitamin D3 from dietary sources is absorbed by facilitated diffusion and

becomes bound to alpha-2-globulin in blood. Cholecalciferol is then enzymatically (calciferol-25-hydroxylase) converted to 25,hydroxycholecalciferol (25-OH-D_3) in the liver. Then 25-OH-D_3 is transported to the kidney, where further metabolism (by 25-OH-D_3-1 hydroxylase) to 1,25 dihydroxycholecalciferol (1,25-$(OH)_2$-D_3) occurs. The conversion of 25-OH-D_3 to 1,25-$(OH)_2$-D_3 is rate-limiting, and partially explains the delay in biological activity of dietary vitamin D_3.

- In the liver, 1,25-$(OH)_2$-D_3 can also be converted by 24-hydroxylase to 24,25 dihydroxycholecalciferol (24,25-$(OH)_2$-D_3). The 24,25-$(OH)_2$-D_3 is less active and is preferentially formed when high serum calcium levels exist. Vitamin D metabolites increase serum calcium concentration in the following ways:
    1. Vitamin D and its active metabolites function to increase the absorption of calcium and phosphorus from the intestines. The major target tissue for 1,25-$(OH)_2$-D_3 is the small intestine where it increases the active transcellular transport of calcium and phosphorus.
    2. The absorptive capacity of the intestine for calcium is a direct function of the amount of calcium binding protein (CaBP) present. Synthesis of CaBP is stimulated by vitamin D metabolites.
    3. The active metabolites of cholecalciferol also act on bone. Vitamin D (in the presence of PTH) is required for osteoclastic resorption and calcium mobilization from bone. Cholecalciferol, 25-OH-D_3 and 1,25-$(OH)_2$-D_3 stimulate osteoclastic proliferation and resorption of bone. On a per weight basis 1,25-$(OH)_2$-D_3 is 100 times more potent in stimulating bone resorption than is 25-OH-D_3.
- Active metabolites of vitamin D also stimulate the retention of calcium by increasing its renal distal tubular reabsorption.

Clinical Signs

- Clinical signs most commonly associated with cholecalciferol-induced hypercalcemia can be divided into neurologic, cardiovascular, gastrointestinal, and especially renal.
- Clinical signs generally develop within 18 - 36 hours postexposure and include: anorexia, lethargy, nausea, weakness, vomiting (± blood), diarrhea (± blood), polyuria, polydipsia, and rarely neurological disturbances (e.g., seizures). Clinical signs become more severe as serum calcium levels increase.
- Hypercalcemia can result in EKG changes including shortened Q-T interval and prolonged P-R interval. Vasoconstriction and hypertension may occur.
- Effects on the kidney include an interference with the ability of the collecting tubules to reabsorb water. Hypercalcemia reduces the concentration of cAMP in cells that normally respond to antidiuretic hormone (nephrogenic diabetes insipidus). Hypercalcemia and hypercalciuria also cause decreased sodium-chloride reabsorption leading to a degree of medullary washout. Clinically, polyuria and hyposthenuria are observed. In dogs with induced hypercalcemia, vasoconstriction of glomerular afferent arterioles occurs with a resultant decrease in GFR.
- Death is thought to result from hypercalcemia, calcification of tissues, and renal and heart failure.

Clinical Pathology

- The most profound alteration in serum chemistry is an elevated serum calcium (more than 11.5 mg/dl in adult). Elevations in serum phosphorous occurred at 12 hours postingestion and preceded serum calcium rise (occurred 24 hours postingestion). Increased BUN and creatinine are also seen.
- Urine specific gravity may be in the hyposthenuric range (1.002 - 1.006). Proteinuria and glycosuria may be seen.
- **Note** - Adjusted calcium values (adjusted for protein binding by albumin) may need to be considered. Corrected calcium = Ca (mg/dl) - albumin (gm/dl) + 3.5. Alternatively, ionized calcium concentrations can be determined directly by many laboratories.
- Condition must be distinguished from normally occurring (physiologic) juvenile hypercalcemia; therefore, a baseline serum calcium determination is generally indicated as soon after ingestion as possible.

Lesions

- Morphological changes seen in dogs given vitamin D experimentally included: roughened, red, raised plaques in aorta or pulmonary artery. Histopathologically, these were characterized by intimal proliferation, subintimal edema, and hemosiderin deposition. Thyroid glands were grossly enlarged and paler than normal, microscopic changes included hypertrophy and hyperplasia of parafollicular (C) cells.

- Lesions associated with renal involvement included kidneys with red and gray cortical surfaces. Calcium deposition was random. Degeneration of renal tubular epithelium was evident microscopically. Mild glomerular degeneration was observed. Mineralization occurred in the basement membrane of tubules, especially the ascending loop of Henle, collecting and distal convoluted tubules occurs. This can be a critical problem since renal tubular epithelium regeneration requires an intact basement membrane.
- Calcification and necrosis of intramural coronary arteries, gastric mucosa, intestinal wall, parietal pleura, terminal pulmonary airways, thyroid, pancreas, and urinary bladder was observed. Myocardial degeneration, necrosis, and mineralization may occur.

Diagnosis

- Based upon exposure history, clinical signs, development of hypercalcemia, and if death occurs, lesions. Differential diagnoses include hypercalcemia secondary to paraneoplastic syndrome (most commonly observed with lymphosarcoma), juvenile hypercalcemia, and hyperparathyroidism.
- Kidney calcium concentration may be in the range of 1,000 parts per million as compared to approximately 100 parts per million for controls.

Treatment for Animals Exposed to Cholecalciferol Rodenticides

- Current recommendations for the control of hypercalcemia are as follows (treatment should be followed in order):
- If patient has recently (< 3 hours) consumed cholecalciferol bait, emesis should be induced.
- Activated charcoal and a saline cathartic are administered depending upon the likelihood of the presence of unabsorbed bait in the digestive tract. Also, repeated doing may be of value in counteracting enterohepatic recirculation of vitamin D and its active metabolites.
- Determine baseline serum calcium levels as soon as the animal is presented if a potentially toxic dose was digested. Continue monitoring serum calcium levels approximately every 24 hours to determine if further therapy is required. If therapy is required, it is continued until, when it is withdrawn, serum calcium levels are found to remain normal.
- Fluid therapy consists of IV normal saline and furosemide (5 mg/kg given IV followed by 2.5 - 4.5 mg/kg TID to QID per os) as a diuretic. Thiazide diuretics should not be used because they decrease urinary excretion of calcium and may contribute to or cause hypercalcemia. Saline is preferred over other fluids, because of enhancement of calcium elimination in the urine.
- Patient should be placed on a low calcium diet (such as s/d, u/d/, or k/d), and sunlight should be avoided.
- Cortisone should be administered (2 - 3 mg/kg). Corticosteroids have several beneficial effects including inhibition of osteoclast-activating factors (OAF) action on bone. In addition, cortisone directly inhibits release of OAF and depresses PG 2 mediated release of OAF. Corticosteroids also exert a hypercalciuric effect and cause decreased intestinal absorption of calcium.
- Calcitonin (salmon calcitonin) has been used in the treatment of hypercalcemia. This is to be given in microgram quantities (4 - 6 IU/kg) SQ every 2 - 3 hours initially until serum calcium levels stabilize. Therapy should be individualized according to need. Long-term calcitonin administration (weeks) at increased doses may be required. Foreign protein reactions are possible necessitating therapeutic administration of epinephrine and possibly other agents as well as discontinuation of further use of calcitonin.
- Pamidronate (Aredia®), a second generation biphosphonate, blocks dissolution of hydroxyapatite and decreases conversion of calcifidiol to calcifitriol. It has a long half life *in vivo*. It can be used instead of calcitonin. Although very expensive, e.g., $300 for one dose for a 25 kg dog, only one to a few treatments may be needed.
- Treatment with diuretics and corticosteroids should continue until the animal's serum calcium concentrations have stabilized in the normal range. Often treatment should continue for 2 weeks, followed by removal of therapy, and retesting of serum calcium levels after 24 hours. Continue 1-week-long regimens of diuretic/corticosteroid until serum calcium remains normal after their withdrawal (check serum Ca^{++} at 24, 48, and 72 hours after final therapy). Monitor serum calciums and BUN as needed throughout therapy.

Case Report

- On 3/4/86, a 3 month old female Rottweiler (12 lb, 5.4 kg) was thought to have eaten approximately 15 grams of Quintox (1/2 packet). On the next day, 3/5/86, the animal was lethargic, vomiting, and had a temperature of 102.5 ºF. The dog was started on IV normal saline and penicillin. WBC = 15,000, PCV = 32, TP = 5.6. On 3/7/86, the dog was depressed, vomiting, had a painful abdomen and difficulty breathing. Urine sp gr = 1.010, BUN too elevated to determine, calcium (uncorrected) = 13.6, WBC = 12,000, PCV = 33, and TP = 5.6. Treatment was changed to normal saline with potassium and bicarbonate IV. IV dexamethasone (Azium) was also administered. Deterioration of the dog's condition continued until 3/10/86 when the owners elected euthanasia. Histopathology revealed tubular degeneration and mineralization of the renal tubules, mineralization of alveolar septa, and focal parenchymal hemorrhage in the lung.

- Total kidney concentrations elevated (300 - 1,000 ppm on wet weigh basis).
- Serum concentrations of cholecalciferol and/or its metabolites may be supportive.

Vitamin D (and Multivitamin Preparations)

Sources

- **Note** - Vitamin D, 40 IU = 1 mcg.
- Many multivitamin preparations contain from 140 - 400 IU Vitamin D and 1,000 - 2,500 IU Vitamin A. Others also contain between 10 - 18 mg elemental iron per tablet.
- Dogs occasionally ingest large (50 - 200 tablets) quantities of the multivitamins.
- Vitamin A and D ointments contain Vitamin A at approximately 1,350 IU/g and Vitamin D at approximately 270 IU/g of ointment.

Toxicity

- The NCR daily recommended requirement of Vitamin D for growing dogs is 22 IU/kg.
- Historically, Vitamin D poisoning had been associated with chronic oversupplementation. Chronically administered (1 - 3 weeks) Vitamin D may cause toxicosis at 2,000 - 4,000 IU/kg.
- Acute Vitamin D toxicosis in the dog has been reported following the ingestion of 64,000 - 460,000 IU/kg.
- **Note** (Regarding multivitamin and iron preparations):
    - Vitamin A toxicosis in humans occurs if Vitamin A is ingested in excess of 25,000 IU/kg.
    - Iron toxicosis may occur if 40 - 60 mg of iron/kg are ingested.

Treatment for Vitamin Supplement Ingestions

- Often none required.
- Emetics, activated charcoal.
- See Treatment section for Animals Exposed to Cholecalciferol Rodenticides.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Organic Compounds
Stillage liquid from ethanol production	Cattle	(Syndrome not yet confirmed)	-	
Carbon tetrachloride	(See Hepatotoxic Chemicals and Drugs)			
Phenolics	(See Hepatotoxic Chemicals and Drugs)			
Carp gallbladders (ingestion, from any of several species of carp; uncooked)	-	-	-	
Diquat (Herbicide)	Most species	Few days	Days to weeks; potentially lethal	

Nephrotoxic Plants

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Vitamin D - Containing Plants

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Cattle, horses, sheep, swine	Weeks to months	Months to permanent damage; potentially lethal	

1. ***Cestrum diurnum*** - Day blooming jessamine, wild jasmine, day cestrum, or Chinese inkberry.

- Member of the nightshade family (*Solanaceae*).

Poisonous Principle

In contrast to other members of this family, *C. diurnum* owes a significant aspect of its toxicity to its content of 1,25-dihydroxy-vitamin D-glycoside.

Toxicity

- Activity of *C. diurnum* is about 3.0 - 10^3 IU vitamin D/kg dried leaf.
- Disease has been produced in pigs fed 3% *Cestrum* leaf meal in the diet and in sheep administered 0.5 g/kg BW per day for 4 days.

Habitat

- Plant was introduced from West Indies. In warmer parts of the USA (California, Texas, Florida, Hawaii), it is grown as an ornamental plant.
- It has escaped cultivation in south Florida.

Susceptible Species

- Poisonings have been reported in Florida in cattle and horses.
- Syndrome has been experimentally reproduced in swine and sheep.

Clinical Signs and Clinical Pathology

- Horses:
  - Affected horses lose weight over a period of 2 - 6 months.
  - Become stiff and are reluctant to move, developing a short, choppy gait. Reluctance to move especially when turning. Flexor and suspensory ligaments are sensitive to palpation.
  - Slight to moderate kyphosis.
  - Elevated pulse and elevated respiratory rates.
  - Clinical signs may reach an end point which can persist for years.
  - In affected animals, serum calcium is elevated (11.4 - 16.7 mg/dl), but serum phosphorus is normal.
- Cattle:
  - Clinical signs of *Cestrum* poisoning in cattle are very similar to those seen in horses. Progressive lameness and chronic wasting predominate. Serum calcium is elevated to values of $\geq$ 14 mg/dl.

Lesions

- Horses:
  - Soft tissue mineralization (calcification) from hypervitaminosis D is widespread in arteries (aorta 2 - 3 fold thickening), ligaments, and tendons. Calcinosis of the forelimb flexor tendons is more severe than the pelvic limb. Suspensory ligaments of all limbs calcified. Renal and lung calcification is **not** a hallmark of this disease. Left atrium is most severely calcified part of heart. Generalized osteoporosis from retarded osteocytic osteolysis has been reported.
  - Emaciation.
  - Parathyroid chief cells (C-cell) hyperplasia.
- Cattle:
  - Osteoporosis and parathyroid chief cell (C-cell) hyperplasia.
  - Soft tissue calcinosis involving tendons, ligaments, and vessels may be similarly involved.
  - Glomerular fibrosis and interstitial fibrosis of the kidneys occur. Hyperplasia of the zona glomerulosa of the adrenal gland.

2. ***Solanum malacoxylon*** -

- Disease has been known as "Manchester wasting disease" and, in Hawaii, "Naalehu disease", (rough translation is "covered with grey ashes").
- The disease syndrome is associated with ingestion of the leaves and stems of the *S. malacoxylon* plant.

Poisonous Priciple

Plant contains a molecule similar to or identical to 1,25-dihydroxy vitamin D with a carbohydrate moiety. The glycoside is then cleaved to the active form of vitamin D *in vivo.*

Toxicity

- Activity of vitamin D in *S. malacoxylon* is about 1.3 X 10^5 IU vitamin D equivalents per kg dried leaf.
- A level of 1.5 - 3.0% dietary *S. malacoxylon* will induce calcinosis.

Susceptible Species

The disease syndrome has been reported in sheep and cattle. Other animals are susceptible experimentally. Adult cows are more susceptible than are calves.

Clinical Signs and Clinical Pathology

- Reported clinical signs include progressive emaciation, joint stiffness, and weakness.
- Serum calcium elevations (as well as a moderate increase in serum phosphorus) occurs.

Lesions

Aortic calcification (intima and media) as well as all major and minor blood vessels occurs. Mineralization of the heart, lungs, and kidneys may also develop. Hyperostosis may lead to bone thickening. A dark basophilic band (possibly mucopolysaccharides) separates new bone growth from pre-existing bone.

3. ***Tricetum flavescens***

Soluble Oxalate - Containing Plants - Beta

Beta vulgaris - Beet, sugar beet, fodder beet, mangel, mangel-wurzel, mangold.
Family - Polygonaceae (buckwheat family).

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Beets (*Beta*) (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	
Curly dock (*Rumex*) (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	
Lamb's quarters (*Chenopodium*) (Soluble oxalate-containing plant) (See Miscellanous Plants that Affect the GI Tract)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	
- *Kochia Scorpia* (Soluble oxalate-containing plant) (See Poisonous Plants that Affect the Liver)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	

Habitat

USA; England; Scandinavia: used as forage, fodder.

Toxic Principle

- Nitrate.
- Oxalate.
- Perhaps another substance.

Susceptible Species

Sheep, cattle, probably others.

Toxicity

- Ingestion of sugar beet tops after the beet roots have been harvested may cause death losses in livestock.
- Concentrations of KNO_3 are as high as 8.8% on a dry weight basis.
- Nitrate concentration may be increased by treatment with 2,4-D.
- Oxalate concentrations may reach 12%.
- Wilting before feeding decreases toxicity, but does not affect the oxalate content.
- Various strains of fodder beets are fed (roots are fed) in England and Scandinavia.

Clinical Signs

- Ingestion of fodder beets has been associated with an increased probability of hypocalcemia in **dairy cattle**.
- In **sheep**, rumen ammonia levels increase after eating beets but ruminal acidosis (overload) seems to be the main concern.

Rheum - Rhubarb

Rheum rhaponticum - Rhubarb, pie plant
Family - Polygonaceae (Buckwheat Family)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	

Description

A stout, perennial herb, 6 - 30 inches high. The stalk has a concave surface on one side, similar to celery, but less pronounced. The leaves are heart-shaped and 20 - 50 cm (8 - 20 inches) long by 20 - 40 cm (8 - 16 inches) wide. The leaves are basal, long stalked and divided on veined, finger fashion; the green or red leafstalks are sheathed. The leafstalks are roundish about 1.2 - 2.5 cm (1/2 - 1 inch) wide, and there are 5 primary veins from the basal leaf. The flowers are greenish-white, numerous, dense and in clusters. Deeply rooted. Roots tend to occur in clumps.

Toxic Principle

- Oxalic acid, calcium and potassium oxalates.
- Possibly other toxic principles.

Susceptible Species

All, especially livestock.

Toxicity

- Oxalic acid is corrosive, and contact may cause skin and gastrointestinal irritation. The leaf blades, and not the edible petioles contain the toxin in quantity. Cooking does not destroy the toxin.
- Swine eating the leaf-blades have died.
- Humans have been poisoned from eating the cooked leaf blades. Only a small amount of the leafblade has caused significant poisoning.
- Rhubarb is considered one of the most dangerous of all plants in a garden.

Signs and Effects

- Swine:
  - Staggering, excessive salivation, vomiting, and death in convulsions.
- Humans:
  - Frequently, there is a lag period of about 24 hours.
  - There is severe pain in the abdomen and accompanying cramps. Nausea, vomiting, and weakness occur.
  - Electrolyte imbalance, especially a refractory hypokalemia takes place.
  - Breathing becomes labored, and muscle tremors occur.
  - Internal bleeding and nasal bleeding may ensue.
  - Renal signs include: oliguria, anuria, albuminuria, hematuria, ketonuria, and increased BUN.
  - Convulsions and coma followed by rapid death may develop. Death has occurred 3 - 5 hours after the onset of clinical symptoms. Tetany may occur if severe hypocalcemia ensues, but frank tetany is rare.

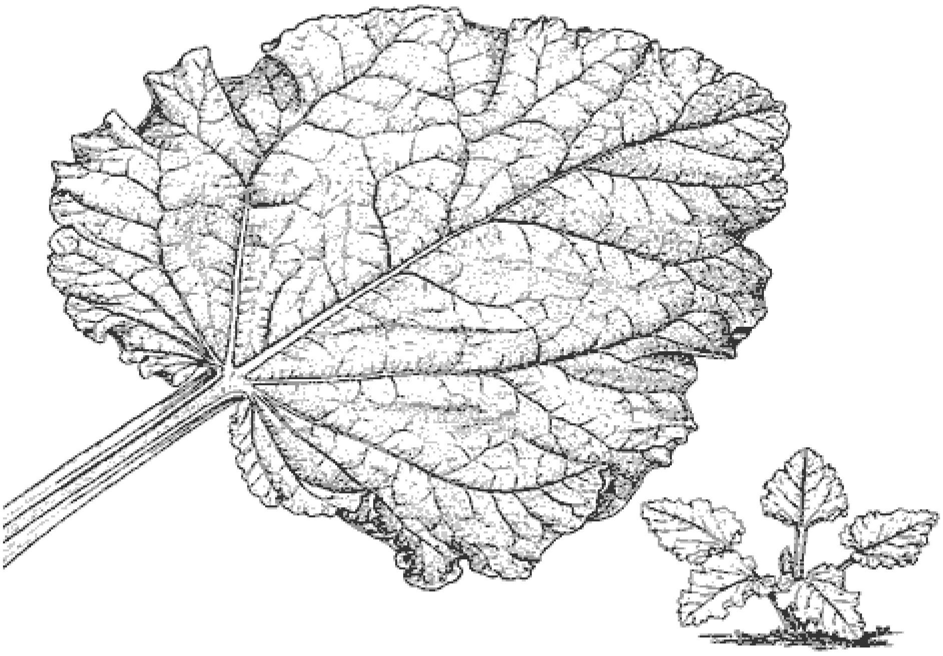
Lesions

- Hemorrhage.
- Oxalate nephrosis especially in the lower nephron; dilated tubules, epithelial degeneration.
- Corrosive changes in the gastrointestinal tract.
- Cerebral edema.

Notes - The petiole (stalk of the leaf) is edible and is commonly used in pies and jams. During WWI, in an effort to conserve food, an official recommendation in England was to utilize the leaf blades as well as the petioles. Severe poisoning and death resulted.

Treatment

Administer oral lime water (calcium hydroxide), milk, calcium gluconate, or calcium lactate. Then, use an emetic if there is **no** evidence of impending convulsions, coma, severe corrosion, or other contraindication. This will tend to form insoluble calcium gluconate before it is brought back up either with the emetic, or by the use of lavage if emesis is contraindicated. Activated charcoal will also be of benefit and a saline cathartic may be used if there is no evidence of corrosive effects. When gastrointestinal effects persist after treatment, however, demulcents, such as milk, should be administered. IV fluids, with added bicarbonate are indicated and the animal should be monitored and managed for renal failure as well as electrolyte imbalances, especially hypocalcemia.



Rhubarb - Note the large fan-shaped leaf blade and fleshy leaf stalk of this excellent pie plant. The flowers and seeds are rarely produced.

Halogeton

Halogeton (Halogeton glomerulatus)

Family - Chenopodiaceae (goosefoot family)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	

Description

- *H. glomeratus*
- Plant - Annual herb, resembling Russian thistle, 1 - 2 ft. tall.
- Stem - Reddish or purplish, branched at base, basal curvature of each branch is characteristic.
- Leaves - In clusters, round, fleshy, wiener-shaped, tipped with a bristle-like hair, 1/2 inch long.
- Fruit - In fall, fruit clusters hide leaves, enclosed in five wing-like brackets.

Habitat

- Native to Eurasia (imported into USA).
- Spreading, especially in Nevada, but also in parts of Utah, Wyoming, Idaho, Colorado.
- In arid and semi-arid regions of the upper intermountain areas of the Rocky Mountains of the USA.
- Overgrazed parts of ranges, along roadways, burned and abandoned fields.
- Salty soils such as dry lake beds.

Toxic Principle

Sodium and potassium oxalates.

Susceptible Species

Sheep, cattle, horses, swine.

Toxicity

- General.
    - 30% oxalate in leaves (dry weight).
    - 10% oxalate in seeds (dry weight).
    - 3% oxalate in stems (dry weight).
    - Excretion is rapid thus the toxic dose must be eaten in a short time for toxicosis to occur.
    - Plants may be more palatable when covered by frost.
    - Poisoning is most frequent in the fall due to the plant's increased toxicity and the decreased amount of other forage availability.
    - 6.9% oxalate is considered nontoxic.
- Sheep.
    - 0.99 - 1.21 g oxalate/kg body weight is lethal if 20 - 30% is absorbed into blood steam.
    - If fed low doses for 4 days, the rumen bacteria become conditioned, resulting in 30% increase in the lethal dose.
    - Sheep fed *Halogeton* (containing 6% oxalate) did not develop a negative calcium balance.

Signs

- Sheep.
    - Chronic cause of death is uremia.
    - Acute death caused by hypocalcemia.
    - Toxicosis is noted within 2 - 6 hours of ingestion.
    - Dullness, weakness, reluctance to move, slobbering.
    - Incoordination, prostration.
    - Labored, rapid breathing.
    - Tetanic contraction of limbs.
    - GI motility is depressed.
    - Convulsions may occur.
    - Coma, shock, and death usually occur within 9 - 11 hours of the onset of clinical signs.
- Cattle.
    - Locomotor difficulty when driven.
    - Frontlegs are more affected than back legs.
- Swine.
    - Diarrhea.
    - May bleed to death from severe GI hemorrhage.

Pathology

- Hemorrhagic rumenitis in some sheep. Gastrointestinal hemorrhage in swine.
- Diagnosis is confirmed by the presence of numerous, nearly transparent crystals in the renal tubules. There is also severe congestion in all parts of the kidney and there may be albumin in the tubules. Renal lesions may be grossly evident, comprised of radially arranged white streaks.

Diagnosis

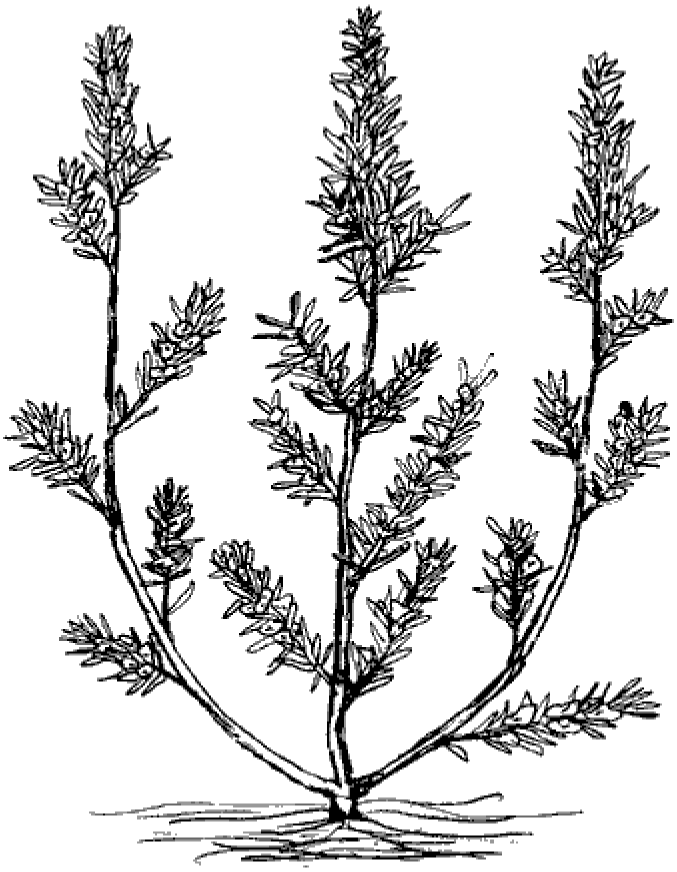
Evidence of consumption of *Halogeton*, appropriate clinical signs, and lesions.

Prevention

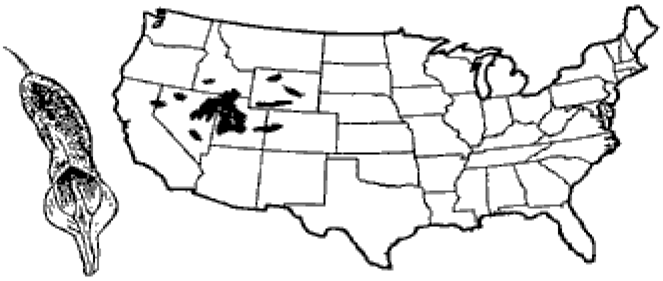
- Oral dicalcium phosphate may be provided for animals likely to ingest *Halogeton* (to form insoluble, poorly absorbed calcium oxalate). Given in ration at 3 parts salt to 1 part dicalcium phosphate-free choice. Or, 5% concentration in alfalfa pellets, 0.25 - 0.5 lb per sheep per day.
- Crested wheat grass will improve range and crowd out the *Halogeton*.
- Treatment of hypocalcemia with intravenous calcium gluconate does not correct all of the clinical signs.

Note

- As oxalate consumption increases, feed consumption decreases.
- In 1962, in one outbreak, 150 cattle died from eating *Halogeton* in Nevada.



Halogeton Glomerulatus



Early Distribution of *Halogeton* (spreading)

Halogeton is often mistaken for Russian thistle. The stems are tinged with red or purple, and are branched at the base. The leaves, which grow in little bunches along the stems, are round, fleshy, and wiener shaped. The seeds are usually enclosed in winglike bracts, which almost cover the plant at maturity. The plant belongs to the goosefoot family. A distinctive characteristic of halogeton is a small single hair, about one-twelfth of an inch long, that grows on the end of each leaf.

Sarcobatus - Black Greaseweed

Sarcobatus vermiculatus - Black greasewood, chico.
Family - Chenopodiaceae (goosefoot family)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal	

Description

An erect, woody, spiny, highly branched, deciduous perennial shrub, which has smooth, whitish bark, becoming grey with age. The leaves are alternate, yellow to bright green, and develop a reddish cast with age. Leaves are narrow, thick, almost round in cross-section, succulent, and 1.2 - 2.5 cm (1/2 - 1 inch) long. The male flowers are cone-like, crowded in a terminal spike and are 1.2 - 3 cm (1/2 - 1.2 inches) long. The female flowers are axillary, inconspicuous and below the male flowers and there is a cuplike calix. The fruit is ovoid, (0.3 - 0.5 cm (1/8 - 1/5 inches) long, surrounded by a pale brown, lobed, peppery, tough wing 0.8 - 1.2 cm (1/3 - 1/2 inches) across.

Habitat

Alberta to North Dakota, South to Texas, California and Mexico, semiarid regions of the Great Basin. Alkaline soils, flatlands, flood plains, dry washes, and gullies.

Poisonous Principle

Sodium and potassium oxalate (4:1).

Susceptible Species

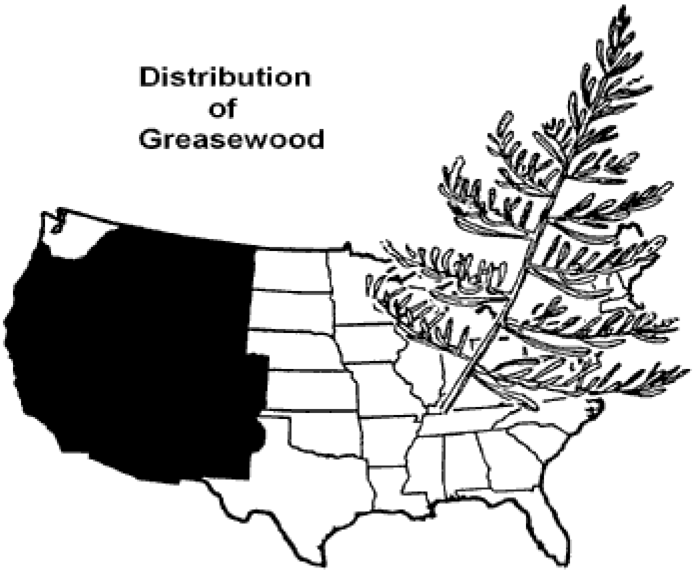
Sheep are more susceptible than cattle.

Toxicity

- The total oxalate concentration varies from 10 - 22% of the dry weight and exists as soluble salts.
- The oxalate content is greatest in the leaves and increases with maturity of the plant.
- Cattle are rarely poisoned under range conditions.
- Oxalate concentrations highest in late summer.

Clinical Signs, Lesions, Prevention

Same as for *Halogeton*.



***Amaranthus* spp. - Pigweed**

Amaranthus spp. - Pigweed

Amaranthus retroflexus - Rough Pigweed, Redroot Pigweed
A. palameri - Redroot Pigweed
A. gangeticus

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Swine, cattle	Days to weeks	Weeks to permanent damage; may be lethal	

Family - Amaranthaceae (Amaranth Family)

Description

- Annual reproducing by seeds
- Stems erect, branching above
- Leaves alternate, simple with long petioles, ovate or rhombic, with a wavy margin.
- Flowers in dense thick spikes, crowded in a close, stiff terminal panicle. Flowers are polygamous, small and green with 3 stiff, spine-like persistent bracts, 4 - 6 mm long; calyx with 5 sepals, 5 stamens, and 1 pistil which is 1-celled.
- Fruit is a utricle, opening with a lid. Seed is lens shaped, ovate, 0.9 - 1.3 mm long, glossy and black.

Habitat

- *A. retroflexus*:
    - Native to the American tropics but now found throughout the USA; especially common in the Midwest. Canada from Prince Edward Island, west to the Pacific Ocean.
    - Roadsides, fields, barnyards, and other areas rich in organic matter; Disturbed pastures.
- *A. palmeri*:
    - Sandy soils of Mexico, California, Arizona, Texas, and southwest Kansas.

Toxic Principle

- Unknown agent causes perirenal edema, nephrosis.
- Oxalate (up to 30%, dry weight): Leaves have 3 times as much oxalate as the stems.
- Nitrate (concentrations at different life stage range from 0.04 to 2.9%).
    - The nitrate content of the plant is fairly constant throughout.
    - Green plant at rapid stage of growth (0.066% KNO_3).
    - Plants that stop growing due to inadequate moisture (0.828% KNO_3).
    - Plants that wilted due to lack of moisture (2.874% KNO_3).
- Hay contaminated by pigweed can be dangerous.

Susceptible Species

- Swine are most often poisoned, especially when newly introduced to the plant.
    - Pigs with continuous access to this plant rarely eat enough to be poisoned.
- Growing calves, cattle.
- Sheep may also be affected.

Clinical Signs

- **Swine** (Perirenal Edema Syndrome).
    - Swine (30 - 150 lb) raised in confinement and given access to contaminated pasture often experience perirenal edema.
    - Posterior incoordination, weakness, trembling, and knuckling at the pasterns with onset at 5 - 10 days after initial ingestion.
    - Affected pigs are alert and appetite usually remains good initially.
    - Later, sternal recumbency, flaccid paresis, especially in the rear limbs; some become unable to rise even when stimulated.
    - The abdomen is often distended.
    - Often pigs subsequently develop coma and die within 48 hours after the onset of clinical signs.
    - Mortality (5 - 50%) has occurred.
- **Cattle**.
    - May also experience nephrosis, dyspnea, and depression.

Lesions

- Retroperitoneal edema in the perirenal connective tissue is the most striking finding in many animals. Edema is often present in the ventral abdominal wall and perirectal area.
- Kidneys are normal or small in size and pale with subcapsular petechiae.

- Edema fluid may be blood tinged.
- Toxic tubular nephrosis, degeration of proximal tubules.
- Necrosis and dilation of the convoluted tubules and a large number of proteinaceous tubular casts, some may have oxalate crystals.
- Calves tend to have more free fluid in the thoracic and peritoneal cavities (straw colored). Renal tubular necrosis and cortical interstitial edema occurs.

Diagnosis

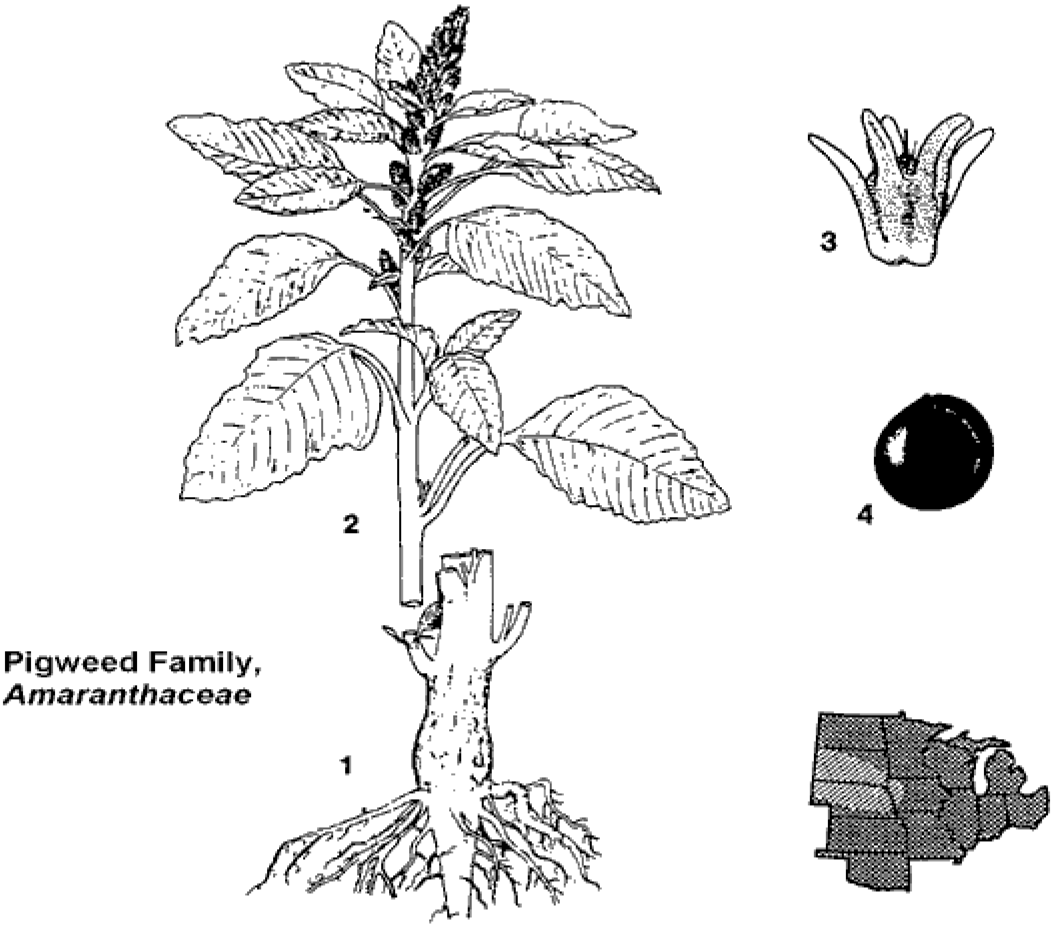
- Identification of *Amaranthus*, evidence of consumption, and appropriate clinical signs and lesions.
- Oxalate crystals in kidneys are **not** a consistent finding.

Treatment

- Remove animal from source of plant insult.
- Less than 10% of animals die after removal.
- Avoid stress, dehydration from any cause.

Prevention

- Mow, then spray with 2,4-D or similar herbicide.
- Spraying plants with 2, 4-D may intensify nitrate accumulation.
- Therefore, remove all animals from pasture for 1 week following spraying to avoid exposure to plants until they have dried out.
- Ruminal microflora may become adapted, thereby facilitating oxalate degradation, but whether this tends to protect cattle from toxicosis due to *Amaranthus* is not known.



Redroot Pigweed, *Amaranthus retroflexus* L. **1**, lower stem and roots; **2**, upper stem with leaves and flower clusters; **3**, flower; **4**, seed. **Annual**, reproducing by seeds. **Taproot** shallow, reddish. **Stems** erect, up to 6 feet (1.8 m) high, rough, branching freely if not crowded. **Leaves** dull green, usually at least 6 inches (15 cm) long when mature, ovate to lanceolate. **Flowers** green, small, in thick, stiff, paniclelike terminal spikes with many short, crowded lateral branches. Bracts much longer than sepals and utricles. Sepals longer than utricle, curved, rounded, often with small notch at end. **Seeds** shiny black, lens-shaped, ovate, notched at the narrow end, about 1mm in diameter. **Found** in cultivated fields, yards, fence rows, and other waste places. Other species, such as smooth pigweed and Powell amaranth, are similar to redroot pigweed in morphology and weedy habits, and may often be found in the same area. Redroot pigweed is also commonly known as rough pigweed.

Quercus - Oak

Quercus gambelii, Q. harvardi, Q. marilandica, Q. stellata, Q. breviloba, Q. coccinea, Q. durandii, Q. pedunculata, Q. prinus, Q. robur, Q. rubra, Q. velutina - Oak

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Esp. ruminants	Days to weeks	Weeks to permanent damage; may be lethal	

Family - Fagaceae (Oak or Beech Family)

Description

- Plant - Woody, perennial, trees, or shrubs.
- Leaves - Alternate, entire, toothed or lobed; persistant or deciduous.
- Flowers - Staminate flowers; pistillate flowers solitary to clustered.
- Fruit - Acorn, 1 seeded, partly enclosed.

Habitat

- All parts of the United States.
- Poisoning may be more common in the southwestern states of Texas, New Mexico, Arizona, and Utah; Europe, New Zealand.
- Common in broadleaf forests, rangelands, dry to wet situations, sandy to limestone to clay soils.

Toxic Principle

- Unknown.
- Probably a gallotannin which is a combination of gallic acid and tannic acid.

Susceptible Species

- Cattle, sheep, goats, rabbits, chickens, guinea pigs, rarely horses.
- Swine seem resistant.

General

- All oaks should be considered potentially toxic.
- Buds, small leaves, flowers, and stems are palatable and poisonous.
- As the leaves mature, they become less palatable and animals are less likely to be poisoned.
- Most cases of poisoning occur when the leaves and buds are young and tender (**spring**).
- Acorn poisoning often occurs during a wet **fall** season following summer drought conditions. Acorn poisoning may occur in the fall or winter.
- Animals must usually eat oak leaves or acorns in large quantities for 2 - 4 weeks or longer prior to the onset of clinical poisoning.
- Animals have been poisoned by drinking water that had oak leaves soaking in it.

Cattle

- Cattle eating *Q. harvardi* in Texas have died within 24 hours after onset of clinical signs; however, animals are usually ill for 5 - 10 days to a month or longer.
- Yearling calves still nursing are usually more susceptible than adults.

Sheep

- Sheep have died within 1 - 3 days after the onset of clinical signs.
- Complete recovery seldom occurs in less than 2 - 3 weeks.

Horses

Poisoning occurs occasionally in horses.

Chickens

A diet containing 0.5% tannic acid produced depressed growth and 5 - 7% mortality in 7 - 11 days.

Clinical Signs:
General Signs and Clinical Pathology Findings

- Abdominal pain, constipation, extreme thirst, edema, depression, frequent urination.
- Bloody diarrhea.
- Rapid but weak pulse.
- Elevated SGOT and SD enzyme activities; elevated BUN, creatinine, potassium.

Subacute Cases

- Atony of rumen, small hard feces.
- Feces may contain blood and black tarry diarrhea may occur in later stages.
- Anorexia, emaciation, weakness, prostration.
- Fast, weak pulse.
- Rough coat, dry muzzle, subnormal temperature, grinding of teeth.

Terminally

- The tail and perineum becomes stained with black feces.
- Hemorrhagic enteritis.
- Bloody feces containing diphtheritic membranes.
- Kidney damage is indicated by elevated BUN levels, lowered urine specific gravity, and poor renal clearance; urine may be dark.
- Death may occur within 24 hours after onset of clinical signs.

Lesions

- Gastritis and nephritis are major lesions.
- Pseudomembranes may form in the intestinal tract.
- Increased amounts of peritoneal and pleural fluids.
- Perirenal edema and hemorrhages with pale, swollen kidneys are characteristic.
- The proximal convoluted tubules of the kidneys may be damaged and abundant hyaline or granular casts may be evident.
- Gut lesions may resemble the "button ulcer" of hog cholera.

Diagnosis

- Identification of *Quercus* spp, evidence of consumption in large amounts, and appropriate clinical signs.
- The kidneys are often large and pale with petechial hemorrhages; elevated BUN, creatinine and serum potassium.

- Mucous and blood are commonly present in the voided feces.

Treatment

- Terminate exposure to oak, acorns, etc.
- Supplement feed.
- Blood transfusions if anemic; fluid therapy.
- Activated charcoal for recent ingestion (repeat daily).
- Avoid water deprivation, stress.

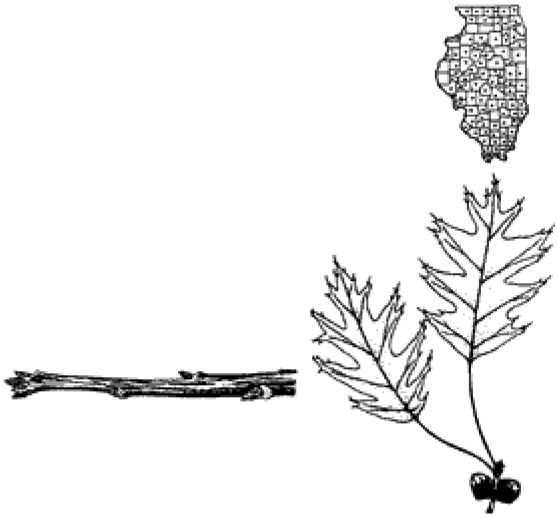
Prevention

- Children should be warned against chewing acorns.
- Cattle - 15% calcium hydroxide can be mixed in a pelleted ration to lessen hazard of acorn ingestion.
  - Cattle-supplement recommendation:
    - 1080 lb cottonseed or soybean oil meal.
    - 600 lb dehydrated alfalfa leaf meal.
    - 120 lb vegetable oil.
    - 200 lb hydrated lime (10% calcium hydroxide).
  - Feed 1 - 2 lb/head/day.

Notes

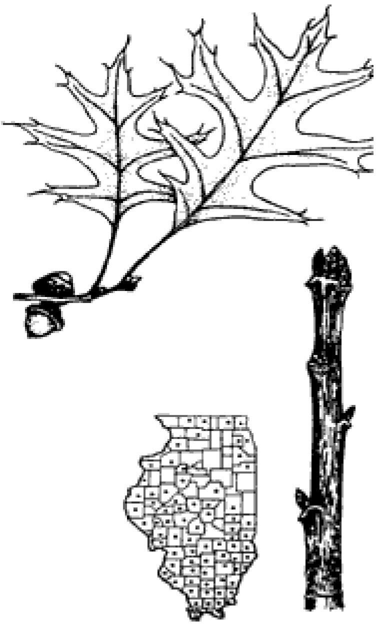
- Cattle losses due to acorns in Missouri usually stop 1 - 2 weeks after a hard freeze.
- In April, 1935: 502 cattle and 426 sheep died in Sutton County, in southwest Texas, from eating leaves and buds of *Q. breviloba*. Drought caused other forage to be nearly absent.
- Annual losses in the southwest may approach 10 million dollars.
- Indians removed the outer shell and ground the kernels into meal, but the meal was then leached many times before eating.

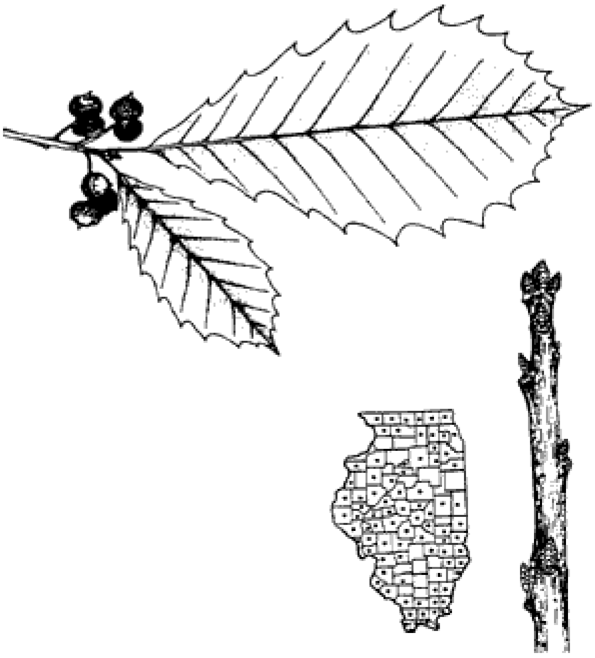
BLACK OAK Yellow-bark Oak.
Quercus velutina Lam.



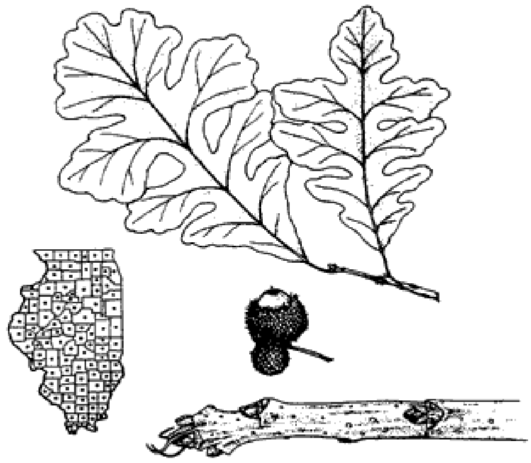
NORTHERN RED OAK
Quercus rubra L.

PIN OAK
Quercus palustris Muench

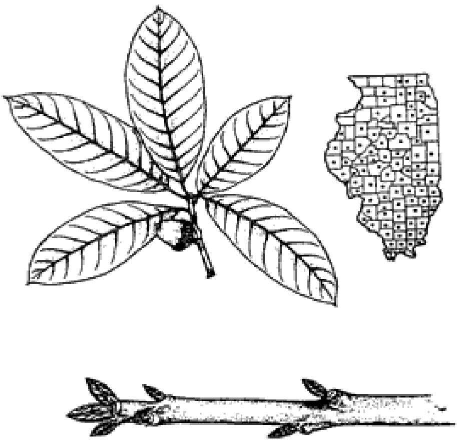




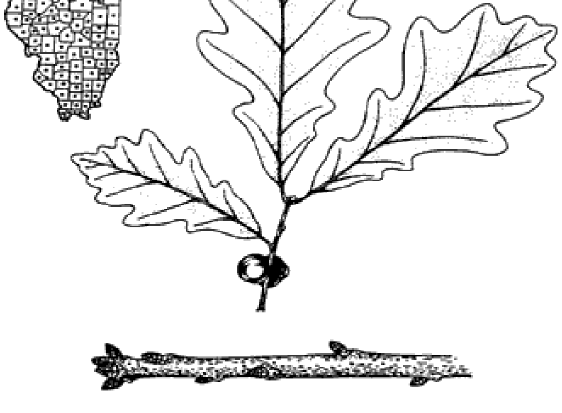
BUR OAK
Quercus macrocarpa Michx.



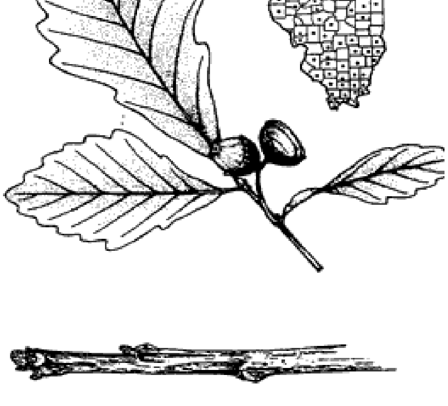
SHINGLE OAK
Quercus imbricaria Michx.



WHITE OAK
Quercus alba L.



SWAMP WHITE OAK
Quercus bicolor Willd.



Lilium and *Hemerocallis* spp.

Lilium longiflorum - Easter Lily
Lilium lancifolium - Tiger Lily
***Lilium* spp.** - Other lilies including Japanese show lily, rubrum lily and Lilium hybrids
***Hemerocallis* spp.** - Day Lily

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Plants
Cats	0.5 - 3 days	Days to permanent damage; often lethal	

Description

Lilium

- Root - Scaly bulb, not truncate, sometimes stoloniferous or rhizomatous.
- Leaves - Linear or lanceolate, whorled, horizontal or with recurred tips. Veins parallel. Petioles short or absent. Stem unbranched. Bulbils form in leaf axils or on lower part of stem.
- Flowers - Solitary and terminal or in terminal raceme or umbel, cup-shaped or bowl-shaped. Up to 30 cm in width 6 segments, spreading or reflexed each with a basal nectar-bearing gland. Six stamens. Fruit a 3-celled capsule containing many flat seeds in 2 rows per cell.

Hemerocallis

- Root - Fibrous or somewhat tuberous often with enlargements at each end.
- Leaves - Basal, linear, keeled, tapered, 2-ranked, usually falcate. Often grass-like.
- Flowers - Ephemeral, in clusters on long scapes, perianth funnelform to campanulate.
- Six segments uniting to form a narrow basal tube. Six stamens. Ovary 3-celled. Fruit a loculicidal capsule with 3 valves.

Habitat

Lilies and day lilies are widely cultivated as ornamentals in gardens and as house plants.

Toxic Principle

Unknown.

Susceptible Species

- Toxicosis has been recognized in the cat.
- There is no evidence at this point, to indicate definitively whether or not other domestic species are sensitive.

Toxicity

Toxicosis in cats has been reported after consumption of leaves or flowers of *Lilium* or *Hemerocallis* spp.

Clinical Signs

Toxicosis in cats results in acute onset of gastrointestinal upset, reduced activity, and anorexia followed by renal failure developing 48 - 96 hours after ingestion. The syndrome appears to be associated with a high mortality rate if the animal is not treated.

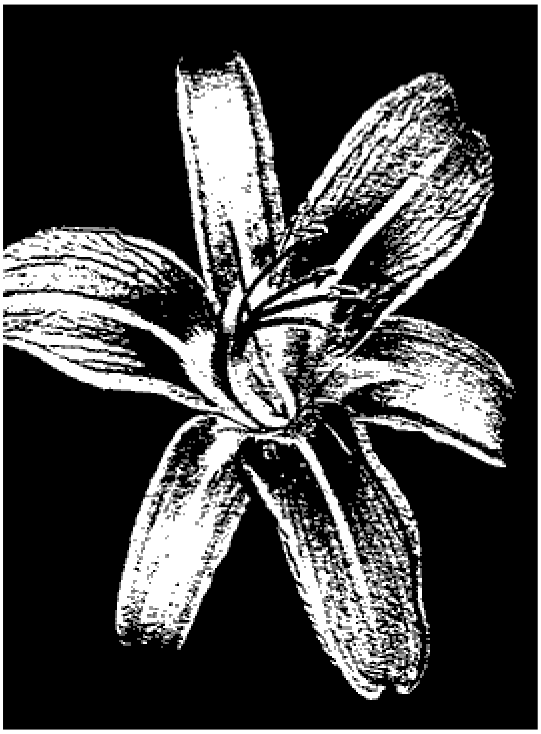
Lesions

Renal tubular necrosis with preservation of the basement membrane.

Treatment

- Induction of emesis.
- Administration of activated charcoal.
- Saline catharsis.
- Fluid diuresis (2 - 3 times maintenance for at least 24 hours).

Notes - Aggressive treatment begun within 24 hours of ingestion (before renal failure occurs) has resulted in nearly 100% survival in preliminary studies. Once renal failure occurs the syndrome is potentially fatal. In one case, a cat survived when treatment was begun after the onset of lily-induced renal failure and the cat was treated via long-term peritoneal dialysis.



Orange Day Lily (*Hermerocallis Fulva L.*)

Family - Lily (liliaceae).
Growth Form - Perennial herbs from fibrous roots.
Stems - Upright, smooth, up to 6 feet tall.
Leaves - Basal, elongated, tapering to a point, up to a 1/2 inch broad.
Flower Arrangement - Flowers several, in terminal clusters.
Flowers - Orange, up to 6 inches long.
Perianth - 6-parted, united below into a tube.
Stamens - 6.
Pistils - Ovary superior; style long and slender.
Fruits - Capsule oblong, smooth, up to 2 inches long.
Habitat - Roadsides and open, disturbed areas.
Range - Throughout the state.
Time of flowering - June to August.
Note - The name Day Lily comes from the fact that each flower opens for only one day.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
				Full Table for Nephrotoxic Plants
Hybrid Sudan or Sudan Grass (*Sorghum* spp.) [Indirect effect of equine cystitis - ataxia syndrome (ascending infections)]	(See Toxicants that Cause Paralysis)			
Cocklebur (Xanthium)	(See Poisonous Plants that Affect the Liver)			

Nephrotoxic Mycotoxins

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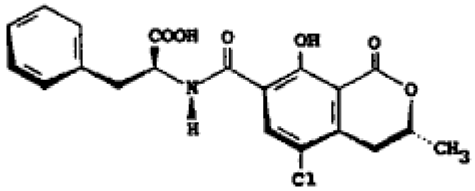
Ochratoxins

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Mycotoxins
Swine, poultry	Days to weeks	Days to permanent damage; often lethal in poultry	

Ochratoxins comprise a series of related metabolites (at least 7 in all) isolated from several species of *Aspergillus* and *Penicillium* molds. Ochratoxins A, B, C, D, and their methyl and ethyl esters have been isolated. Ochratoxin A is thus far believed to be the most toxic and most common of the ochratoxins.

Sources

Ochratoxin is primarily a contaminant of feed grains and cereals. The toxin occurs in barley, sorghum and especially wheat. It has also been found in corn, dried beans, rye, oats, mixed feeds, and peanuts.



Ochratoxin A

Occurrence

- Ochratoxin A is presumed to be the cause of porcine nephropathy seen in Denmark, Sweden, and the USA.
- Production by *Penicillium viridicatum* occurs at temperatures as low as 4 ºC and with a moisture content of the affected grain of 18.5 to 40.4%.
- Concentrations reported in Denmark were as high as 27.5 ppm in barley.
- During the porcine nephropathy epidemic in Denmark, over 50% of the barley had 0.2 ppm; and 0.2 ppm can cause experimental nephropathy in pigs.
- Has often been detected in Swedish barley and oats as well as in Japanese rice.
- Was found in one hay sample and six wheat samples (at up to 6 ppm) from Western Canada.
- Detected in concentrations (1.0 to 2.7 ppm) believed to be toxic to swine and cattle in Iowa.
- In 1976, ochratoxin was believed to be the biggest problem occuring in poultry in North Carolina.
- Occurrence generally tends to be sporadic.

Susceptible Species

Potentially hazardous to livestock. Toxicity has been demonstrated in swine, ducklings, chickens, turkeys, and dogs.

Toxicity

- Synergistic or additive effects with aflatoxin, citrinin or penicillic acid (other mycotoxins) (see below).
- The toxicity of ochratoxin A is approximately equal to that of ochratoxin C, although ochratoxin A is much more commonly encountered. Ochratoxin B is several times less toxic.

Species	Ochratoxin A Oral LD50 mg/kg
Chicken	2 to 4
Turkey poult	6
Japanese quail	16.5
Rat	22 to 30
Mouse	22 to 58

- **Swine are very sensitive**. Doses of 1 to 3 mg/kg in swine caused considerable gastrointestinal and lymphoid damage.
- In swine, ochratoxin A at 1 or 2 mg/kg BW caused toxicosis, and death occurred within 5 to 6 days.
- Also in swine, dietary concentrations of 1 ppm for 3 months caused polydipsia and reduced growth rate and feed conversion in addition to impaired renal function.
- In swine microscopically detectable renal lesions were induced by as little as 0.2 ppm of ochratoxin in the diet.
- **Cattle are reportedly** extremely **resistant** to ochratoxin A, **but calves are sensitive** until the rumen is developed. Thirty-day-old calves given 0.1 to 0.5 mg/kg/day for 30 days displayed polyuria, CNS depression, decreased weight gain, urine of low specific gravity and dehydration.
- In calves, an approximate lethal dose is between 11 and 25 mg/kg BW while doses of 0.1 to 0.5 mg/kg produced only polyuria.
- A dose of 3 mg/kg BW **in dogs** produced acute toxicosis.
- In dogs, doses of 0.2 to 0.4 mg/kg caused clinical signs to develop over 10 to 14 days, while no clinical signs developed during 21 days of dosing at 0.1 mg/kg.
- In rats, average doses of 210 and 70 µg/kg (5 days/week) for 2 years caused decreased weight gains on the order of 12% less than controls and decreased urine concentrating ability, decreased kidney weights and renal tubular epithelial damage.
- Ochratoxin A has been shown to be teratogenic in rodents.
- **Chickens are very sensitive**. Decreased growth and enlarged kidneys occurred in chickens fed ochratoxin A at 1 ppm in the diet.

Interactions with Other Mycotoxins

- Ochratoxin may prevent fatty liver resulting from alfatoxin exposure (poultry). In the same study, however, the combination of ochratoxin and aflatoxin caused greater inhibition of growth when compared to aflatoxin alone.
- Doses of ochratoxin alone and penicillic acid alone, neither of which were lethal, caused 100% deaths when given simultaneously.

Mechanisms of Action

- Ochratoxin A may exert most of its effects as an inhibitor of protein synthesis. Ochratoxin inhibits protein synthesis by competition with phenylalanine in the phenylalanine-tRNA synthetase reaction.
- The kidney and spleen were more sensitive than the liver with regard to ochratoxin-induced protein synthesis inhibition.
- Ochratoxin A is immunosuppressive, causing decreased immunoglobulin production.
- Ochratoxins inhibit bovine carboxypeptidase A.
- Ochratoxin A is taken up by mitochondria and appears to inhibit several aspects of mitochondrial respiration.
- In the liver, ochratoxin A causes increased glycogen deposition in the cytoplasm of hepatocytes, and this increase is a sensitive indicator of ochratoxicosis.
- Low ochratoxin doses generally result in increased hepatic glycogen content, while high doses of the toxin cause decreased hepatic glycogen.
- In chickens fed ochratoxin at 2 to 8 ppm in the diet, there is a loss of collagen in the large intestine which may result in breaks and loss of integrity in the affected gut.
- Ochratoxin A is a potent cause of decreased carotenoid pigmentation of chickens; the loss of yellow color from the fat of chickens decreases marketability.

- Even at 1 mg/gm (1 ppm) of diet the egg shells of chickens are stained; at higher concentrations, there are reductions in egg production, egg shells are poor or rubbery and the kidneys are damaged.
- The probability of hemorrhage may be increased by a multifactorial coagulopathy affecting factors VIII, V, and X in chickens.
- At 2 ppm and greater (dose related) in birds there is a decrease in breaking strength of bones and an increase in broken bones.
- Ochratoxin A has been associated with urinary tract cancers, but it is only weakly mutagenic.
- Ochratoxin A is a potent teratogen. Mice and/or rats exposed via their dams experienced malformations, fetal death, and occasional brain necrosis. Deformities also has been noted in hamsters and chickens, but not in pigs.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Ochratoxins bind serum albumin (protein bound).
- Ochratoxin A is toxic *in vivo* and *in vitro*, suggesting that the molecule does not require metabolic activation to exert its effect. Pretreating an animal with phenobarbital to increase P-450 activity will cause an increase in the LD_{50} (lower sensitivity of the animal due to faster detoxification).
- The only metabolic reaction of ochratoxin A so far identified, is hydrolysis by carboxypeptidase A to break an amide bond. The reaction produces ochratoxin-alpha, which is much less toxic than the present compound. This reaction is especially prevalent in ruminant protozoa, and it is estimated that it allows cattle to tolerate up to 12 ppm of ochratoxin A in their feed.
- Ochratoxin A is believed to be hydrolyzed to a significant degree in the functional rumen.
- In spite of the ruminal destruction of some of the ingested ochratoxin, large doses reportedly result in some ochratoxin excretion in milk and may be associated with renal failure in cattle (see below).
- Whether differences occur among their cattle with regard to the ability of rumen flora to convert ochratoxin A to ochratoxin α, or whether other nephrotoxic mycotoxins may coexist, in hazardous concentrations, with ochratoxin A should be investigated.
- Ochratoxin A binds strongly to the proximal tubules of the kidney. Pigs exposed to ochratoxin A accumulate the toxin in the kidney, liver and muscle (in decreasing order) and these present the basis for some concern regarding residues (up to 67 ppb detected in kidneys) in human food products.
- The approximate half-life of ochratoxin A in swine tissues is 3 to 5 days, and little or no ochratoxin can be detected in kidney 30 days after exposure is terminated.
- In sheep, fetal blood concentrations are 100 to 400 times lower than maternal blood concentration.

Signs

- One disease syndrome described in swine was termed endemic porcine nephropathy. Porcine nephropathy was initially recognized in Denmark and Sweden, but cases have been seen in Iowa swine in several instances.
- Although high doses **in swine** may cause gastrointestinal effects as well as liver and lymphoid damage, **much more common is the chronic renal failure syndrome**.
- Acute exposure to ochratoxin A generally causes anorexia, polydipsia, dehydration and depression. Continued intake of toxic levels causes reductions in rate of gain and feed efficiency. Diarrhea may occur.
- Primary clinical signs include:
  - Polydipsia
  - Polyuria
    - Dilute urine
  - Reduced gain and feed efficiency
  - Cattle may be similarly, but much less commonly affected as compared to swine.
  - Human endemic nephropathy in the Balkan countries (Yugoslavia, Bulgaria, Romania) of Europe (termed Balkan Endemic Nephropathy) has been associated with ochratoxin contamination of cereals and swine tissues. Other mycotoxins and other risk factors are also being investigated.
  - Areas of high incidence of Balkan Nephropathy also have high rates of urinary tract cancer.
  - Renal, hepatic, and mammary gland tumors were noted in laboratory rodents in response to dietary ochratoxin A exposure.
- In turkeys, one bite of ochratoxin containing feed causes immediate feed refusal, although this does not occur similarly in the chicken.
- In poultry, reduced egg production and egg shell quality may be seen.

Clinical Pathological Findings and Lesions

- Changes vary with the severity and duration of the syndrome.
- Acute toxicosis.
    - Clinical pathology.
        - Increased PCV and hemoglobin.
        - Increased blood urea nitrogen, total protein, and the activities of lactic dehydrogenase, isocitric dehydrogenase and aspartate aminotransferase.
        - Increasingly dilute urine, with increases in urine glucose and protein, and increases in urinary enzymes such as leucine aminopeptidase.
    - Lesions vary with the dose and duration of exposure.
    - Gross lesions in acutely poisoned animals may include:
        - Dehydration.
        - Enteritis.
        - Gastric and intestinal hyperemia.
        - Pale, swollen kidneys.
- Microscopic lesions in the acute form may include:
    - Proximal tubular (especially the P3 segment) necrosis and dilation.
    - Focal areas of intestinal mucosal damage in the lower intestine.
    - Prolonged exposure of animals to low levels of ochratoxin A causes a primary problem of nephropathy.
    - Exposure to high doses of ochratoxin A causes nephrosis, enteritis, lymphoid necrosis and hepatic necrosis.
    - A similar nephropathy in cattle fed ochratoxin-contaminated feedstuffs was also reported in Iowa.
    - Birds may have visceral gout and nephrosis.
- Gross lesions after chronic exposure may include:
    - Few lesions except for greyish white kidneys that are firm, and may have cystic dilation at the cut cortical surface.
    - Potential urinary tract tumors.
- Microscopic findings in the chronic form may include:
    - Mild degenerative changes in the tubular epithelium of the kidneys with prominent dilated tubules and interstitial fibrosis, and tubular atrophy. Basement membranes may be thickened and sclerosis of the glomeruli may be seen. The tubular epithelial nuclei become enlarged and nuclei become enlarged and necrotic. Thickened basement membranes may occur and dilated tubules with flat tubular epithelial cells may be seen.
    - Birds may have urate crystals and nephrosis with more chronic effects than in the acute form. Other lesions encountered experimentally were mentioned with regard to Mechanisms of Action (above).

Diagnosis

- Change of feed prior to the onset of illness.
- Feed may be moldy but this can be difficult to recognize due to differences between different areas of the feed and due to inability to recognize mold damaged feed after milling.
- Polydipsia, polyuria.
- Appropriate lesions, especially in the kidneys.
- Poor egg production with poor, stained, or rubbery shells in chickens.
- Detection of ochratoxin in the feed in toxic concentrations.
- Detection of ochratoxin-alpha in kidney, liver and skeletal muscle.
- Urine and feces may also be analyzed for ochratoxin.

Treatment

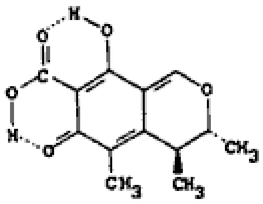
- Best to avoid in the first place by properly drying grains and storing feeds. The use of mold inhibitors can also be of value.
- In acutely exposed animals, such as dogs, appropriate measures to evacuate the gastrointestinal tract may be used with adsorbents and saline cathartics as indicated to remove ochratoxin containing feedstuffs.
  Note - Not likely for animals to be presented with only a known recent exposure to ochratoxin, but might know of recent ingestion of mold-damaged grain or feed.

- Supportive care should be similar to that for other causes of renal failure.

Citrinin

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Nephrotoxic Mycotoxins
(may coexist with, and potentiate the effect of, ochratoxins)			

Citrinin is probably a mycotoxin in search of a disease. In other words, the toxin has been recognized for several years, has known toxicity, primarily affecting the kidneys but is not known to actually cause clinical toxicosis.



Citrinin

Toxicity

- Generally the toxicity of citrinin is low enough that concentrations found in naturally contaminated feedstuffs do not approximate those necessary to cause experimental toxicosis.
- LD$_{50}$s range from 19 to 110 mg/kg in various species, using various routes of administration.

Significance

- May interact and coexist with ochratoxin and might potentiate the toxicity of the latter.
- May also coexist with other toxins such as patulin and oxalic acid.

Section VII: Toxicants that Cause Goiter

Toxicants that Cause Goiter

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Goitrogenic Substances

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Goiter
Iodine	Horses	Chronic	Months	
Soybean (*Glycine*) (rare)	-	-	-	
Flax linseed (*Linum*)	(See Toxicants that Inhibit the Function of Respiratory Pigments)			
Castor bean (*Ricinus*)	[See Plants that Affect the Gastrointestinal Tract, Lectins (Toxalbumins)]			
Sulfonamides	(See Toxicants that Affect the Kidney)			

Introduction

- **Goiter** - Defined as any nonmalignant enlargement of the thyroid gland as a whole, may be accompanied by either hypo- or hyperthyroidism. the enlargement may be due to an increase in the amount of thyroid tissue (hyperplasia), or due to an increase in the amount of colloid causing a distension of acini. Inflammatory proliferation occurs less commonly.
- **Hyperplastic goiter** - Hyperplasia is the first morphologic response to iodine deficiency. With reduced thyroxine production the pituitary releases increased amounts of thyrotropic hormone, which is the stimulus for hyperplasia.
- **Goitrogenic substances** - Any substance which can lead to an increase in the size of the thyroid gland. Included in these are thiouracil (therapeutically used to treat hyperthyroidism), glucosinolates, cyanides, sulfocyanates, thiocyanates, and some sulfonamides.
- Certain plants are known to be goitrogenic when consumed. Included in these are soybeans and members of the Brassicas (cabbage, rape, kale, and turnips). Goitrogenic substances from these plants have been transmitted through the milk (glucosinolates). Cooking, heating, or processing (e.g., soybeans) destroys the goitrogenic substances in these plants.
- Glucosinolates are -D-thioglucoside glycosides found in members of the genus Brassica. The primary significance of glucosinolates in animal nutrition is that oils from these plants are occasionally used as protein supplements. The glucosinolates are hydrolyzed by the enzymes glucosinolase or thioglucosidase. The enzymes required for this activation are present in the plant and are produced by ruminal microorganisms.
- A major effect of the hydrolysis products of glucosinolates is inhibition of the thyroid gland.
  Antithyroid agents have 4 general effects:
  1) they may interfere with iodine uptake by the thyroid gland (e.g., thiocyanate),
  2) can interfere with tyrosine iodination,
  3) suppress thyroxine secretion, or
  4) function as a metabolic antagonist to thyroxine in the tissues.
- **Colloid goiter** (simple goiter) is characterized by enlargement and distension of the acini (which are filled with colloid). The colloid contains very little iodine and thyroxine, symptoms are those of hypothyroidism. Milder goitrogenic substances (e.g., soybeans) are likely to cause this type of goiter.

Iodine Deficiency

- Iodine deficiency results in hypothyroidism and goiter, especially affecting fetuses and neonates of deficient sows, cows, sheep, and goats. **Primary iodine deficiency** results from inadequate dietary intake of iodine.
- **Conditioned iodine deficiency** results from the ingestion of high levels of calcium or goitrogenic plants (e.g., members of the genus Brassica).

Clinical Signs

- Iodine deficient cows have depressed reproductive function, e.g., increased anestrus.
- Cows, sheep, goats, and sows may resorb fetuses, abort, or produce stillborn or poorly viable offspring. Affected neonatal animals have complete or partial alopecia.
- Myxedema and decreased weight gain has been reported in piglets.
- Calves and lambs may have grossly enlarged thyroid glands. Death is common.

Equine Goiter Due to Iodine Toxicosis

Described (1968) in Thoroughbred mares and foals. Has been closely related to increased levels of iodine (due to the addition of dried seaweed). Measured dietary iodine levels were 48 - 432 mg/day/mare. Iodine intake on a control farm (no evidence of thyroid enlargement) was estimated as 6.3 - 7.0 mg/mare/day. Disease syndrome was predominately seen in foals; which were born weak and died in the early postnatal period. Thyroid glands were grossly enlarged. Several mares also had visible goiters. (Baker HJ, Lindsey JR. Equine goiter due to excess dietary iodide. J Am Vet Med Assoc 1968; 153:1618-1630.)

Other Goitrogens - Key Features

- Other goitrogens include:
- Soybeans (*Glycine max*)
  - Of greater concern is trichloroethylene extracted soybean-oil-meal which exerts its effect on the bone marrow causing damage similar to that associated with bracken fern in cattle.
- Flax, linseed (*Linum* spp.)
  - Of greater concern than the goitrogenic effect is the hydrogen cyanide content of flax (See Toxicants that Inhibit the Function of Cytochromes).
- Sulfonamides
  - Of greater concern is the renal failure associated with sulfonamides.
- Castor bean (*Ricinus*).

Brassica and Related Genera, *Brassica* spp.

(Rape - Canada - Cabbage, Kale, Mustards, Related Plants)
B. hirta - White Mustard (Yellow)
B. kaber - Charlock, Wild Mustard
B. napobrassica - Rutabaga, Yellow Turnip, Swede Turnip
B. napus - Rape (note rapeseed meal in brown in color)
B. campestrus - Canola (note canola meal is yellow in color)
B. oleracea var. acephala - Common Kale
B. oleracea var. capitata - Cabbage
B. oleraceal var. botrytis - Broccoli
B. rapa - Turnip
B. oleracea var. gemmifera - Brussel Sprouts
B. nigra - Black Mustard
B. juncea - Indian Mustard
B. pekinensis - Chinese Cabbage
Erysemum cheiranthoides - Wormseed Mustard
Raphanus raphanastrum - Wild Radish
Thlaspi arvense - Fanweed, Field Pennycress

Barbarea vulgaris - Yellow Rocket, Wintercress
Amoracia lapathifolia - Horseradish

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Goiter
Horses	Chronic	Months	

Family - Cruciferae

Poisonous Principles

- Most serious problems arise from glucosinolates or their breakdown products. Glucosinolates are glycosides of B-D thioglucose. The aglycones of these compounds can yield an isothocyanate, thiocyanate, nitrile, or similar compound.
- Canola = at least some varieties such as Tower and Candle are reportedly low in glucosinolates and double zero varieties are low in both glucosinolates and erucic acid (*B. campestrus*)
- Isothiocyanate = causes severe gastroenteritis (*B. hirta, B. kaber, B. napus, B. oleracea, B. nigra, B. juncea, Erysemum cheiranthoides, Raphanus raphanastrum, Thlaspi arvense, Barbarea vulgaris, Amoracia lapathifolia*).
- Goitrogenic = due to goitrin (L-5-vinyl-2-thiooxazolidone), a breakdown product of glucosinolates. This compound inhibits incorporation of I into precursors of thyroxin and interferes with iodine secretion. Rapeseed or forage may cause thyroid enlargement, increased ^{131}I uptake by the thyroid, and decreased blood thyroid hormones in animals fed the milk of exposed lactating females. Placental transfer also can occur (*B. napobrassica, B. napus*, *B. oleracea* var. *acephala*, *B. oleracea* var. *capitata*, *B. rapa, B. pekinensis*)
- Hemolytic = due to S-methyl cysteine sulfoxide (*B. napobrassica*, *B. oleracea* var. *gemmifera*, *B. napus, B. oleracea* var. *acephala*, *Thlaspi arvense*)
- Nitrate = converted to nitrite in rumen (*B. napus*).
- Rapeseed may also cause pulmonary emphysema, reversible blindness, and hepatic necrosis which may be accompanied by photosensitization. The hepatic necrosis, as well as bile duct hyperplasia, and megalocytosis of the kidney tubular epithelium are believed to result from nitriles that may form from the glucosinolates in rapeseed meal (*B. napus*).

Sources

- Forage and root brassicas are widely grown in Britain, and to a lesser extent in Canada, Sweden, and the USA to be used as winter feeds for cattle and sheep.
- Most serious economic problems in livestock seem to result from rapeseed meal.
- **Note -** Other glucosinolate-containing oil meals of minor economic importance include crambe, mustard, and limnanthes (meadow foam) meals.

Glucosinolate Toxic Principles and Mechanisms of Action
(Incompletely Worked Out)

Metabolism

1. Glucosinolates → Allyl isothiocyanates that act as GI irritants, vessicants
2. Oxazolidinethiones (L-5-vinyl-2-thiooxazolidinethione) that are goitrogenic (antithyroid effect)
3. Nitrates→ Nitrites that oxidize hemoglobin to methemoglobin.
4. Nitriles cause poor growth, liver, kidney damage, enzyme induction in liver.
5. Thiocyanates inhibit I uptake by the thyroid.
6. S-methylcysteine sulfoxide

   ↓

   metabolism

   ↓

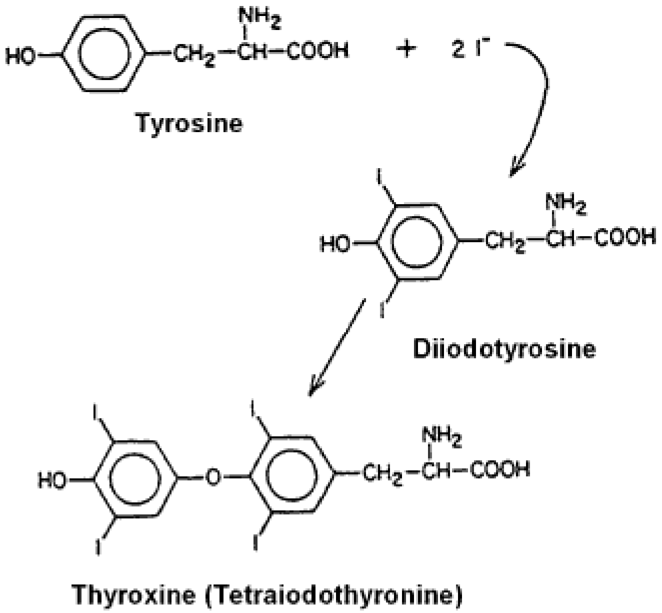
   Dimethyl disulfide

   ↓

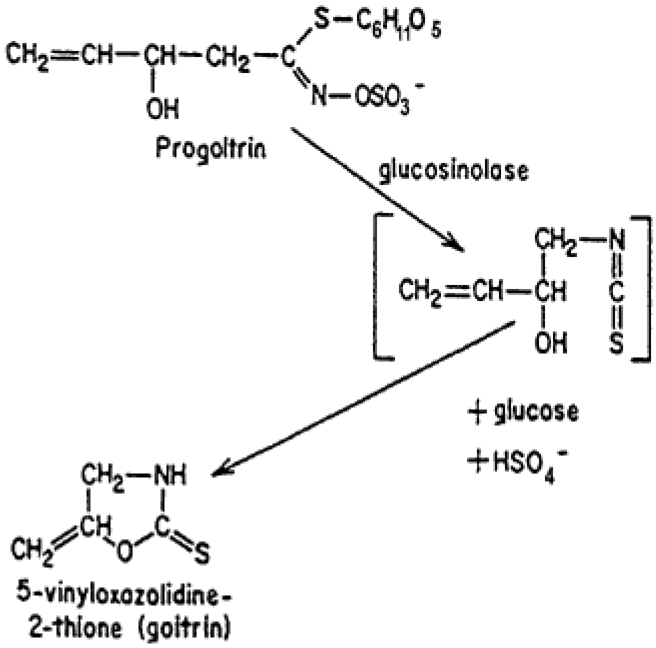
   Also oxidizes hemoglobin → Hemolytic anemia

   (A Heinz body anemia)

Normal production of thyroxine from tyrosine



Conversion of progoitrin to goitrin



Susceptible Species

Poultry and swine fed raw rapeseed meal exhibit enlarged thyroids and growth depression. Liver hemorrhage in poultry fed rapeseed meal may be caused by nitrites. Swine may have enlarged livers when fed rapeseed meal.

Toxicity

- Levels of 5 - 10% rapeseed have been tolerated by nonruminants. Ruminants can tolerate 10% dietary rapeseed meal with no ill effects.
- "Double zero" varieties can be fed at much higher rates without reducing animal production.

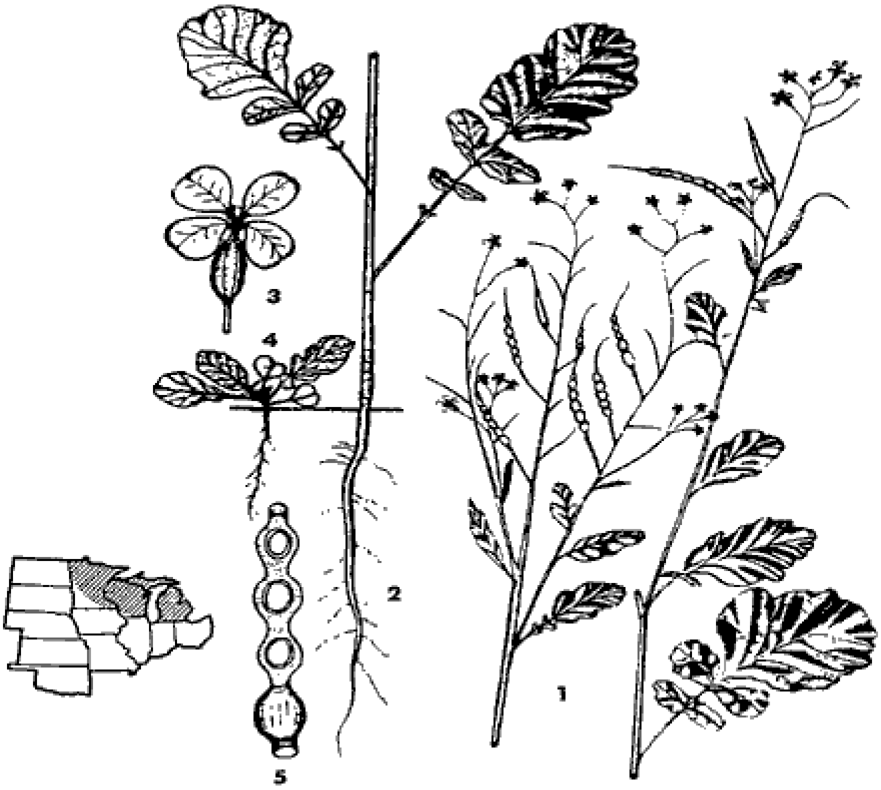
Signs

- Problems of anemia and gastrointestinal upset are noted most often. Reproductive failure and goiter are more insidious.
- Scouring.
- Rumen stasis.
- Jaundice.
- Decreased milk production.
- Growth retardation.
- Poor conception, poor growth, enlarged thyroids; possibly due to antithyroid factors and anemia.

Lesions

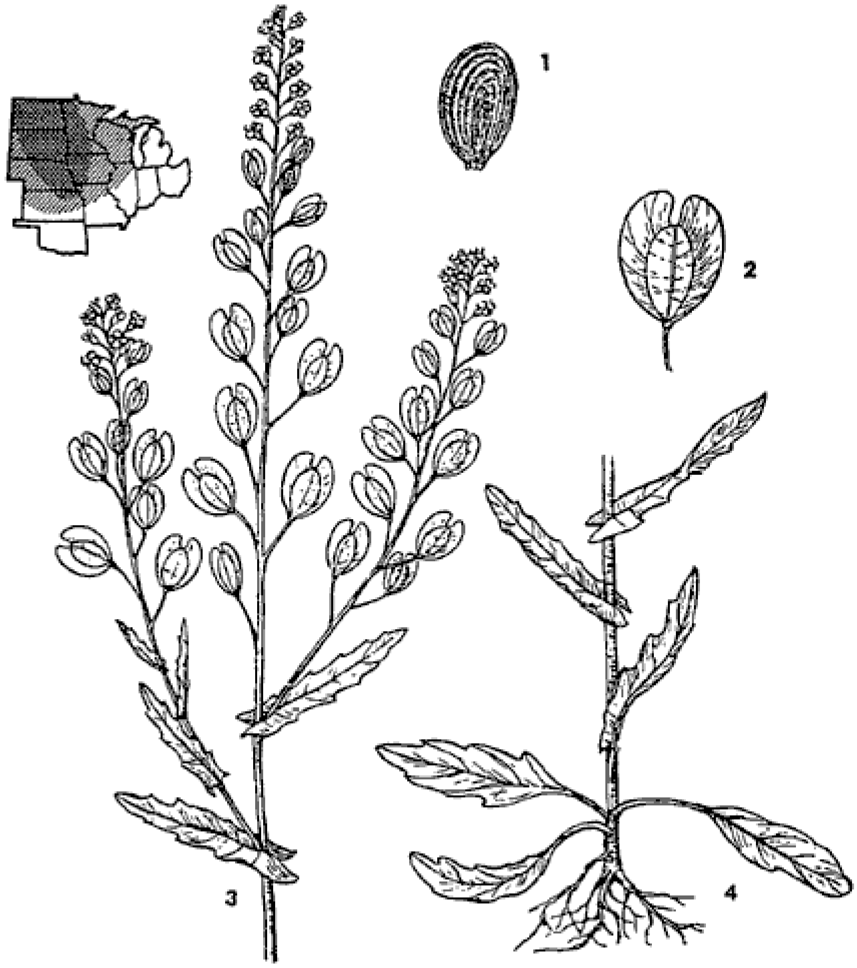
- Liver swollen, pale, or (in poultry fed rapeseed meal) hemorrhagic.
- Hepatic necrosis.
- Extensive hemosiderosis, e.g., spleen, kidney.
- Kidneys dark brown, renal tubular epithelial degeneration, hemosiderin deposition (hemolysis).

Mustard Family, *Cruciferae*



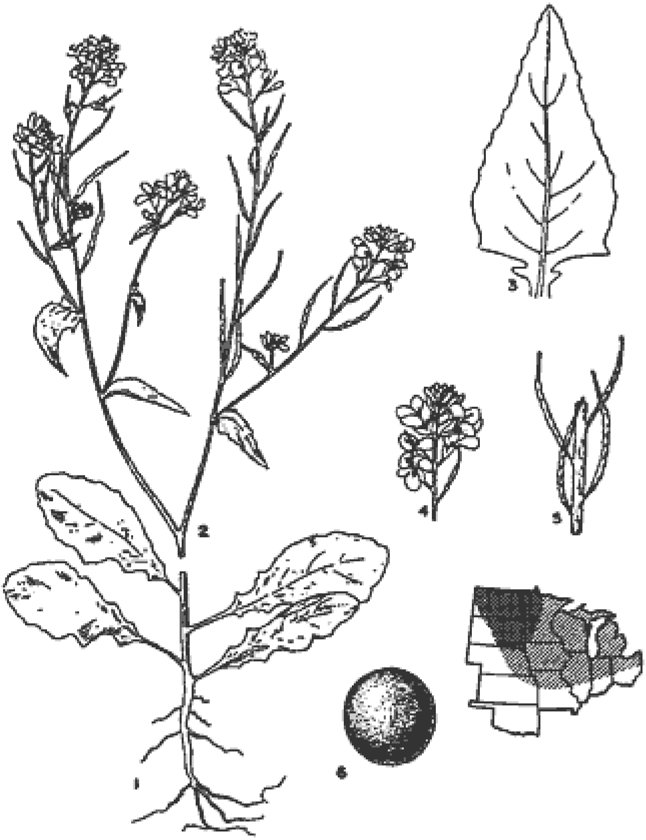
Wild Radish, *Raphanus raphanistrum* L. **1**, upper part of plant with pods and flowers; **2**, lower part of plant; **3**, flower; **4**, seedling plant; **5**, pod with section. **Annual** or **winter annual**, reproducing by seeds. **Stems** erect, branching above, 1 to 3 feet (30 to 90 cm) tall, sparsely pubescent with stiff hairs, especially on lower parts. **Leaves** on lower stem with same type of pubescence, pinnately divided with a large rounded terminal segment. Upper leaves mostly undivided but with a few small segments. **Flowers** light yellow, shading into a whitish or purplish color, 1/2 inch (1.3 cm) in diameter, with 4 petals**. Seed pods** pithy and solid, 1 1/2 to 3 inches (3.8 to 7.5 cm) long, 1/8 inch (3mm) in diameter, at maturity breaking into segments containing seeds. Lower pods usually small and seedless. **Seeds** vary in size and shape but are usually oval, slightly flattened, light reddish-brown, and 3/16 inch (4.5 mm) in diameter. **Found** in small grain and flax crops, where it is serious; also common in wastelands. Pod segments containing seeds are hard to remove from seed grain.

Mustard Family, *Cruciferae*



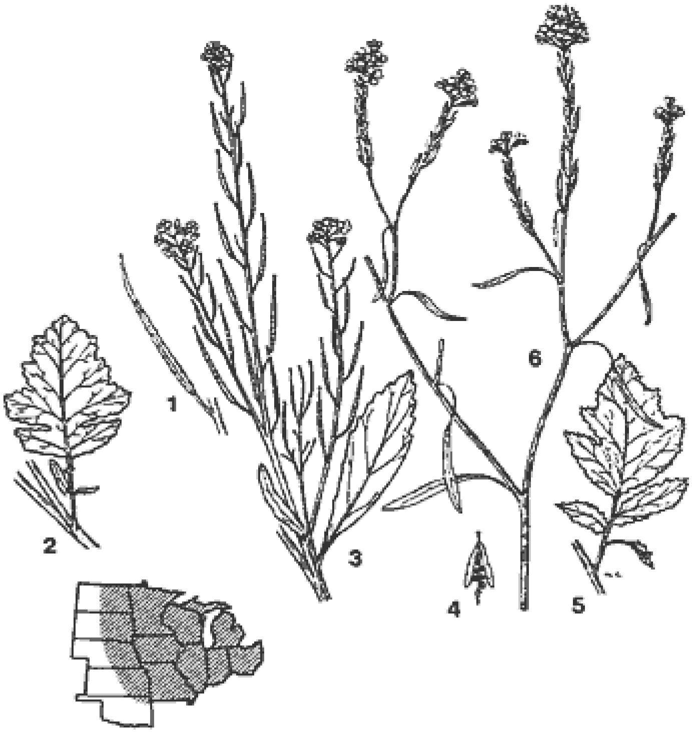
Field Pennycress, *Thlaspi arvense* L. **1**, seed; **2**, seed pod; **3,** upper part of plant; **4**, lower part of plant. **Annual** or **winter annual**, reproducing by seed. **Stems**, erect, 4 to 20 inches (10 to 50 cm) tall, simple or sometimes branched above, smooth throughout. **Leaves** alternate, simple, toothed, 1/2 to 2 inches (1.3 to 5 cm) long, clasping stem with earlike projections.. **Flowers** white with 4 petals, in racemes which lengthen greatly at maturity. **Seed pod** flat, circular, about 1/2 inch (1.3 cm) in diameter, 2-valved, broadly winged, with a deep, blunt notch at the top. Each pod contains several seeds. **Seed** dark reddish-brown to black, ovate in outline, flattened, about 1/16 inch (1.5mm) long with about 10 curved, granular ridges on each side. **Found** in small grains, legumes, and noncultivated areas. This weed imparts a bitter, garlicky flavor and odor to milk.

Mustard Family, *Cruciferae*



Wild Mustard, *Brassica Kaber* (DC.) Wheeler. **1**, lower part of plant; **2**, upper part of plant; **3**, leaf from upper part of stem; **4**, flower cluster; **5**, seed pods; **6**, seed. **Annual** or **winter annual**, reproducing by seeds. **Stems** erect, branched near top, with a few bristly hairs. **Leaves**: lower ones irregularly lobed, toothed, with petioles and with bristly hairs; upper leaves smaller, often not lobed, alternate, with no petioles or short ones. **Flowers** conspicuous, with 4 yellow petals, in clusters at the end of branches. **Seed pod** slender, on a spreading stalk; 1 inch (2.5 cm) or more long, about 1/3 of length being an angular beak at the tip. **Seeds** round, black, bluish, or brown, smooth and hard, about 1/16th inch (1.5mm) in diameter. **Found** commonly in grain fields and occasionally in other cultivated crops. A troublesome weed in many areas. Seeds live in the soil for many years. Also commonly known as charlock.

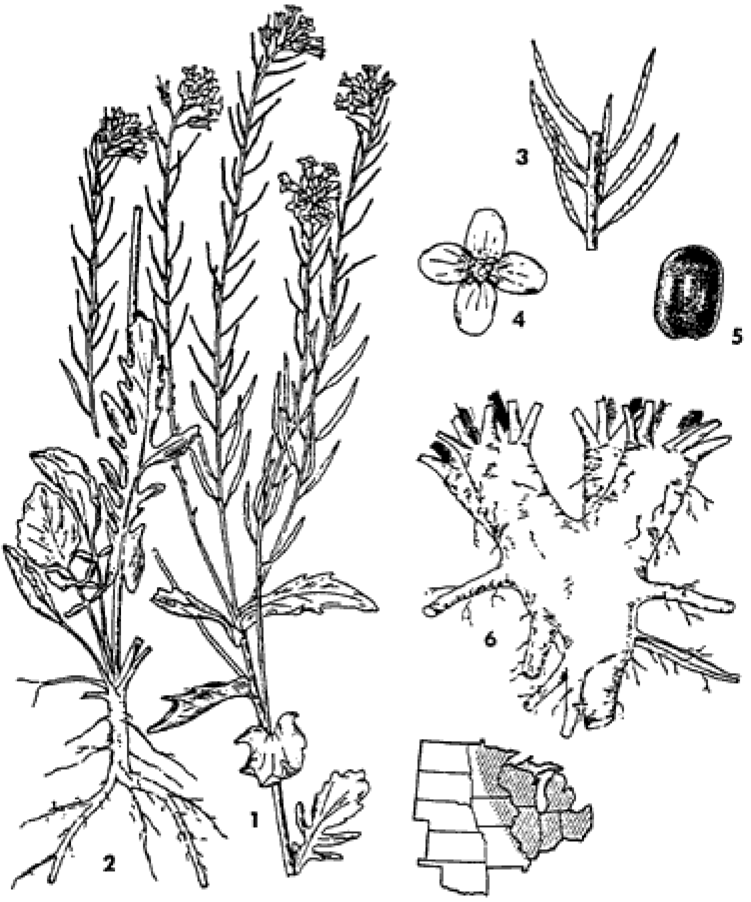
Mustard Family, *Cruciferae*



Indian Mustard, *Brassica juncea* (L.) Coss. **1**, seed pod; **2**, lower leaf; **3**, upper part of plant. **Annual** or **winter annual** with taproot. **Stems** smooth, erect, usually growing 2 to 3 feet (60 to 90 cm) tall. **Leaves**: upper ones short-petioled, lance-shaped, tapering gradually from a broad base; lower ones petioled, deeply lobed, leaf margins coarsely toothed. **Flowers** yellow, with 4 petals. **Seed pods** 1 to 2 inches long, tips conical. **Seeds** rounded, reddish-brown, surface pitted. **Found** in small grain and legume fields.

Black Mustard, *Brassica Nigra* (L.) Koch. **4**, seed pod; **5**, lower leaf; **6,** upper part of the plant. **Annual**, with taproot. **Stems**, erect, branched, growing commonly between 3 and 6 feet (0.9 and 1.8 m) tall; lower parts somewhat hairy. **Leaves** also somewhat hairy. Upper leaves narrow with elongated petiolelike base. Lower leaves petioled, divided, wth large terminal lobe, leaf margins fine-toothed. **Flowers** yellow, with 4 petals. **Seed pods** 1/2 to 3/4 inch (1.3 to 1.9 cm) long, lying along stem. **Seeds** somewhat oval, dark reddish-brown, their suface pitted. **Found** commonly in waste areas and fields.

Mustard Family, *Cruciferae*



Yellow Rocket, *Barbarea Vulgaris* R. Br. **1**, upper part of plant; **2**, lower part of plant; **3**, pods; **4**, flower; **5**, seed; **6**, root. **Winter annual, biennial**, or **perennial**, reproducing by seed, taprooted. **Stems** numerous, growing from a crown, upright, 1 to 2 feet (30 to 60 cm) tall, branched near top, smooth, and angular or rided. **Leaves** pinnately divided; basal leaves have a large termianl lobe, are 2 to 8 inches (5 to 20 cm) long, and form a dense rosette; stem leaves become progessively shorter with top leaves about 1 inch (2.5 cm) long and less deeply lobed. **Flowers** bright lemon-yellow, 4-petaled (typical mustard flower), borne in spikelike racemes on end of each branch. Bloom in late April and early May. **Pods** about 1 inch (2.5 cm) long, about 3/32 inch (2.4 mm) in diameter, nearly square in cross section. **Seeds** light yellow to yellowish-brown, 1/32 inch (0.8 mm) long, ripening in May and early June. **Found** along roadsides, in pastures, and in timothy, clover, and alfalfa fields, where it matures before the crop is cut. Seeds live several years in the soil. Also known as winter cress.

Section VIII: Toxicants that Affect Reproduction

Teratogenic Agents

V. Beasley

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Veratrum

Veratrum californicum - False or Western Hellebore
Veratrum viride - Wild Corn, Skunk Cabbage
Veratrum japonicum - Corn Lily

Major Species	Usual Effects	Full Table for Teratogenic Agents
Sheep, cattle	In sheep: causes "monkey face", cyclops, anophtalmia, cleft palate; shortened maxilla, arthrogryposis, shortened long bones	

Description

- *Veratrum* spp.
    - Plant - Coarse, erect, herb, 1 - 2 m tall (3.9 feet).
    - Stems - Unbranched, leafy throughout.
    - Leaves - 15 - 30 cm long (6 - 12 inches), 7.5 - 15 cm wide (3 - 6 inches).
    - Flowers - Numerous relatively inconspicuous.
    - Rootstock - Thickened, short, perennating.
- *Veratrum viride*
    - Plant - Coarse, perennial, herb, 9.1 - 24.4 dm tall (3 - 8 feet).
    - Stem - Unbranched.
    - Leaves - Alternate, oval, elliptical, or lanceolate, in ranked groups up the stem, 1.5 - 3.0 dm long (6 - 12 inches), wide (6 inches), sheath stem.
    - Flowers - Nnumerous, greenish-yellow, glandless, hairy; in large terminal cluster, 2.0 - 6.1 dm long (8 - 24 inches); lower panicle branches tends to droop.
    - Rootstock - Numerous, coarse, fibrous, thick, vertical.

Toxic Principle

- Primarily glyco-alkaloids. The alkaloids are:
    1. Tertiary amine bases and related esters, or
    2. Secondary amine bases and their glycosides.
- Toxic alkaloids present include: Jervine, veratrosine, pseudojervine, isorubijervine, veratrin, cevadin, veratridin, veradridene, sabadillio.
- Teratogenic alkaloids include: Cyclopamine, veratramine, cycloposine and jervine.
- **Note** - Cyclopamine is believed to be most important due to its greater concentration in plants.

Susceptible Species

- Sheep.
- Cattle often graze the same areas but rarely eat *Veratrum*.

Toxicity

- General.
    - All parts are toxic, especially the roots.
    - Roots and rhizomes are 8 - 10 times more toxic than the tops, but contain less teratogenic agents.

    - Teratogen content of leaves and stems decrease rapidly in late summer, and varies among ranges.
    - 1.8 g of dried *V. californicum* per kg body weight was toxic; 5 g was lethal to sheep; much less is required to cause congenital deformities.
    - Danger of poisoning is greatest in spring when growth is young and succulent.
    - Large amounts are required to produce death, but small amounts will produce clinical signs.
    - Poisoning is seldom acutely fatal due to rapid vomiting and poor intestinal absorption.
- **Sabadilla - Veratrum** (derivative).
    - Acute oral LD_{50} in rats is over 4000 mg/kg.

Signs (*Sabadilla - Veratrum*) in Humans

- General.
    - Salivation, burning of mouth, nausea, vomiting, diarrhea, stomach pain, headache, prostration, hallucinations dyspnea, shallow breathing, weakness, paralysis, spasms, blurred vision, diplopia, confusion, convulsions, slow pulse, or rapid, thready pulse, low blood pressure except with large doses. Low temperature. Transient depression and bronchiolar constriction. Death due to asphyxiation.
- Chronic exposure can produce irritation to mucous membranes of the nose.
  Unpleasant taste, salivation.

Signs - Plant Exposure

- Contact with leaves may cause dermatitis.
- Sheep (Toxicosis).
    - Clinical signs first appear in 2 -3 hours.
    - Excessive salivation purgation, diuresis.
    - General muscular weakness, incoordination.
    - Vomiting.
    - Slow irregular heart rate, slow labored breathing.
    - Cyanosis.
    - Prostration, convulsions, paralysis.
    - If lethal dose is consumed, death will occur in 6 - 18 hours.
- Sheep (Malformations) (Primary problems).
    - More important than acute toxicosis are the cyclopian type "monkey faced" congenital malformations in lambs as well as anopthalmia, cleft palate, hare-lip.
    - Deformities arise in early autumn when flocks of sheep are on mountain meadows containing false hellebore: 10 - 15% of the ewes are barren the next lambing season and 1 - 25% of deformed lambs die. Economic loss is appreciable.
    - These deformities arise from ewes eating the plant during the 12th to 14th day of gestation.
    - Inadequate development of the fetal pituitary glands may result in prolonged gestation. Unusually large fetuses cause dystocia, leading to death of the ewe and fetus.
    - The **types of deformities are directly related to the stage of fetal development** at the time of poisoning.
        - 0 - 10 days - No obvious effect, although some investigators suspect failure to implant and abortion occurs.
        - 12 - 14 days - Cyclopian-type malformations.
        - 12 - 34 days - Motor nerve paralysis.
        - 24 - 30 days - Cleft palate.
        - 25 - 36 days - Hypoplasia of metacarpals and metatarsals.

Mechanisms of Action

- General.
    - The primary action of alkaloids are to **lower blood pressure** and **decrease heart rate**. Increase activity from thoracic chemoreceptors and pressor receptors to inhibit sympathetic outflow and augment vagal influence. Extracts of *Veratrum* are potent ruminatorics, emetics, and cause hypotension, decreased heart rate, increased peristalsis, and hyperglycemia. Veratrum alkaloids have been rarely used as hypotensive agents in human medicine.
    - Tertiary amines cause a myotonic response in skeletal muscles and positive inotropic effect on the heart.

    - Ester alkaloids elicit a reflex decrease in heart rate and blood pressure.
    - Secondary amine bases and glycosides antagonize positive chronotropic action of epinephrine in the mammalian heart.
- Teratogenesis.
    - The exact mechanism of teratogenesis is not known although a selective inhibition of mitosis at the neural plate stage of embryogenesis is suggested.

Lesions

- Lesions of acute toxicosis are not widely reported in naturally exposed animals.
- Malformations of cyclopian-type with hydrocephalus, hair-lip, cleft palate, and displacement of the nose are common.
- Usually the pituitary gland is absent.
- Fetuses exposed at a later stage of development may have shortening of the legs.

Diagnosis

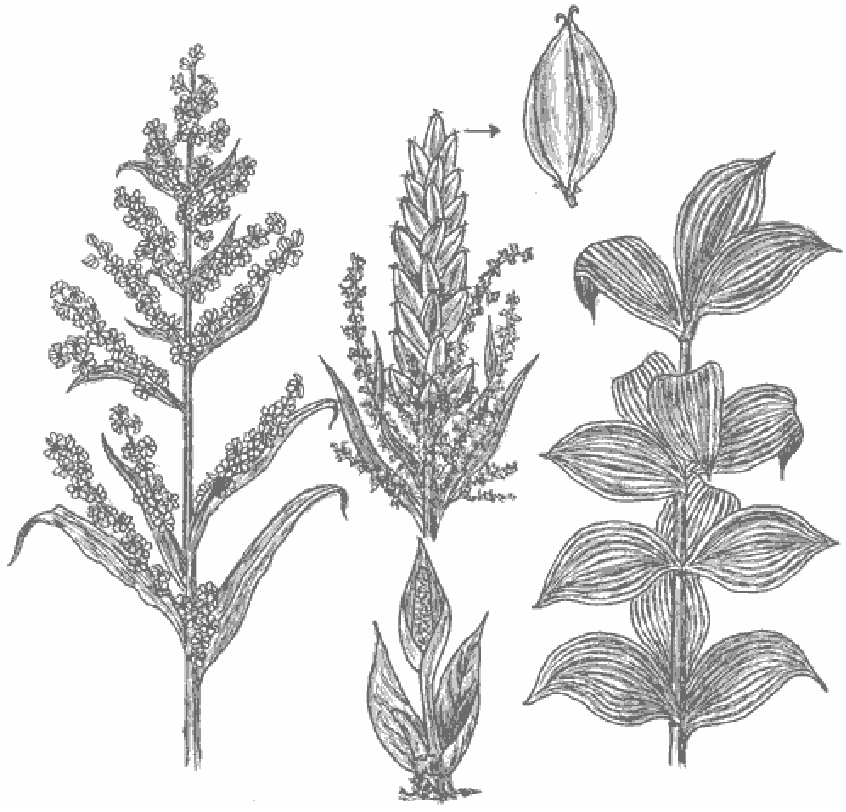
Identification of *Veratrum*, evidence of consumption, and appropriate clinical signs and/or especially malformations.

Treatment

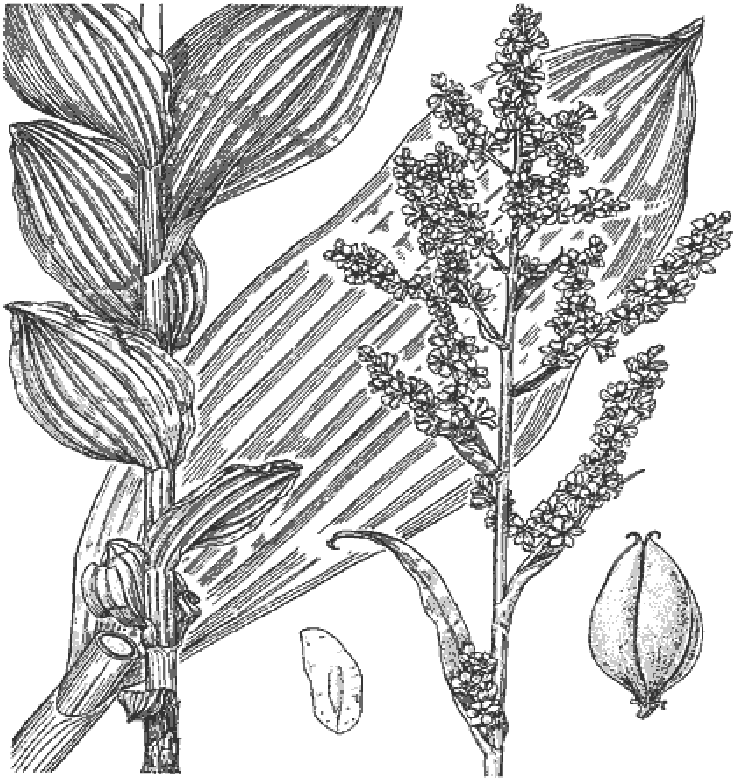
- Remove animal from access to the plant.
- If animal is left undisturbed, it will usually recover in 3 - 4 hours after onset of clinical signs.
- Unless severe toxicosis has occurred, leave animal undisturbed.
- Administration of oxygen.
- Establish respiration.
- Induce emesis unless contraindicated.
- Endotracheal intubation preceding gastric lavage.
- Activated charcoal and a saline cathartic (magnesium sulfate).

Prevention

- *V. californicum* is killed by frost, losses to monkey-faced lambs may be eliminated by delaying breeding until after the first frost, or by preventing access to plants during the critical periods of fetal development.
- Breed ewes 5 weeks before putting them on range containing *Veratrum*.
- Comments.
    - Deformities resulting from *V. californicum* and thalidomide drug are the first 2 documented accounts of mammalian monstrosities in epidemic proportions.
    - Root has been used for medicinal purposes as well as for an insecticide.



American white hellebore
(*Veratrum viride*)



California False-Hellebore - *Veratrum californicum*. Note the large parallel-veined clasping leaves, the large clusters of flowers, the 3-lobed seed capsule (enlarged, lower right), and seed (enlarged, lower center) of this conspicuous plant.

Other Teratogens

Specific Agents	Major Species	Usual Effects	Full Table for Teratogenic Agents
Tobacco (*Nicotiana*) (Plant with nicotinic as well as teratogenic alkaloids)	Swine, cattle	Arthrogryposis, spinal curvature, torticollis	
Poison hemlock (*Conium*) (Plant with nicotinic as well as teratogenic alkaloids)	Swine, cattle	Arthrogryposis, other skeletal malformations, cleft palate	
Lupine, bluebonnet (*Lupinus*) (Plant with nicotinic as well as teratogenic alkaloids)	Cattle, sheep	Arthrogryposis, other skeletal malformations, cleft palate	
Locoweed (*Astragalus* and *Oxytropis*)	Herbivores, sheep	Arthrogryposis, or contracted tendons	
Hybrid Sudan or Sudan grass (*Sorghum*)	Herbivores	Ankylosis, contracted tendons	
Lathyrism (*Lathyrus* spp.)	Herbivores	Various skeletal deformities	
Potato (*Solanum tuberosum*)	Hamster	Spina bifida, exencephaly	
Fescue (*Festuca* with ergot alkaloids produced by the endophytic fungus *Acremonium coenophialum*)	Horses	Dystocia with thick placenta, and oversize, weak foals with overgrown hooves	
Mercury	All species, especially cats	Hypoplasia of the cerebellum and other brain defects	
Organotins	Wildlife in aquatic ecosystems	Skeletal malformations, defective myelinogenesis	
Selenium	Poultry, waterfowl	Hypoplasia of upper and/or lower beak, hindlimbs, wings, and eyes	
Halogenated dibenzodioxins and related halogenated aromatics	Laboratory animals, predatory water birds	Cystic kidneys, cleft palate. Crossed beaks in cormorants	
Vitamin A and derivatives such as isotretinoins	Humans, swine, rabbits, other species	Shortened limbs, altered gait, spinal column abnormalities, cleft palate, malformed ears, craniofacial bone and brain anomalies, microphtalmia	
Corticosteroids	Dogs, possibly other species	Cleft palate	

Griseofluvin	Cats	Cyclops
Thalidomide	Human beings, lab rodents	Hypoplasia of the limbs (phocomelia)
Cocaine	Human beings	Severe neurologic impairment
Ethanol	Human beings	Shortened palpebral fissures (eye opening is small relative to the globe) and ocular problems, premaxillary abnormalities resulting in a flattened midface and an indistinct philtrum. Low birth weght, learning impairment, mental retardation, and microencephaly. Hearing impairment and ears rotating posteriorly. Gait abnormalities, scoliosis, shortened digits. Atrioventricular septal defects. Renal disorders. Threshold dose is only 1 ounce of alcohol/day (causes reduced birth weight). Overall, 5.9% of human newborn babies are affected by some degree of fetal alcohol syndrome.
Other teratogens	-	-

Abortion Inducing Toxicants

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Pinus - Pines

Pinus ponderosa - Western yellow pine, ponderosa pine
Pinus contorta - Lodgepole pine
Pinus taeda - Loblolly pine

Major Species	Usual Time of Abortion	Other Considerations	Full Table for Abortion Inducing Toxicants
Cattle, sheep	Less than 2 days to 2 weeks after initial exposure	Single feeding may cause abortion	

Class - Conopsida (Gymnosperms)

> *Pinus taeda* (Loblolly pine) is a light-reddish barked tree. The needles are in bundles of 2 or 3 and it grows in the South East of United States. Needles used for bedding were reported to be lethal to cattle that ate them.

Ponderosa Pine

Description

> Yellowish-green needles, 7 - 11 inches long in groups of 3. Subterminal, ovoid cones, 2 1/2 - 6 inches long.

Habitat

> East of the Cascade Mountains; California to British Columbia, east to Idaho and Rocky Mountains; South Dakota; Western Canada. Dominant forest member of coniferous forests at moderate elevations.

Toxic Principle

- Isocupressic acid is the primary abortifacient compound. Also, two derivatives, acetyl- and succinyl-isocupressic acid which also occur in pine needles are hydrolyzed in the rumen to form isocupressic acid.
- Toxin present in green and dried needles and is water soluble.
- Anti-estrogenic activity suggested from lab animal studies.

Susceptible Species

- Cattle; sheep less susceptible; deer and cattle from pine-free areas are reportedly more likely to be affected.
- Experimentally, mice are susceptible.

Toxicity

- Cattle.
    - Cattle browsing on needles and buds of this pine are predisposed to abortion.
    - During winter, cattle may consume fallen needles even when other forage is available (January through April).

    - 2.5 - 3 kg of fresh pine needles per head per day produced 75% still-births or weak calves which died shortly after birth. Many of these were premature.
    - A water soluble substance depresses uterine weight.
    - Pelleted pine needles lose their toxicity.
    - Pregnant cattle may abort after eating a single feeding of pine needles.

Signs

- Mice: abortion often killing the dam.
- Cattle.
    - **Last trimester, abortions** are seen in late fall, winter, and early spring.
    - Abortions are most likely to occur when cattle are under stress. Animal's condition is a big factor in determining individual susceptibility.
    - Cows show depression and dullness prior to abortion.
    - Impending abortion may be signaled by edema of the vulva and udder.
    - Abortion usually occurs 2 days after pine needles have been fed but may occur up to 2 weeks after removed from source.
    - **Retained placentas**, manual removal is associated with excessive hemorrhage and often is unsuccessful.
    - Live born calves are weak.
    - Parturition may be characterized by weak uterine contractions, incomplete dilation of the cervix and uterine hemorrhage. Metritis may occur.
    - Live aborted calves have poor viability.
    - Death in cows can occur prior to or after abortions, especially without treatment for secondary complications.

Lesions

- Unborn calves that die in early stages of pregnancy can be resorbed by the mother.
- Aborted fetuses (may die *in utero*) may have necrosis of the proximal renal tubules and moderate thickening of the interlobular septae in the lungs, pulmonary congestion and hemoglobin breakdown.
- Cows may exhibit ecchymotic hemorrhage on the peritoneum, pleura and viscera with an edematous uterine wall.

Diagnosis

Identification of *Pinus ponderosa*, evidence of consumption during gestation, and appropriate clinical signs.

Treatment

Remove animal from access to plant.

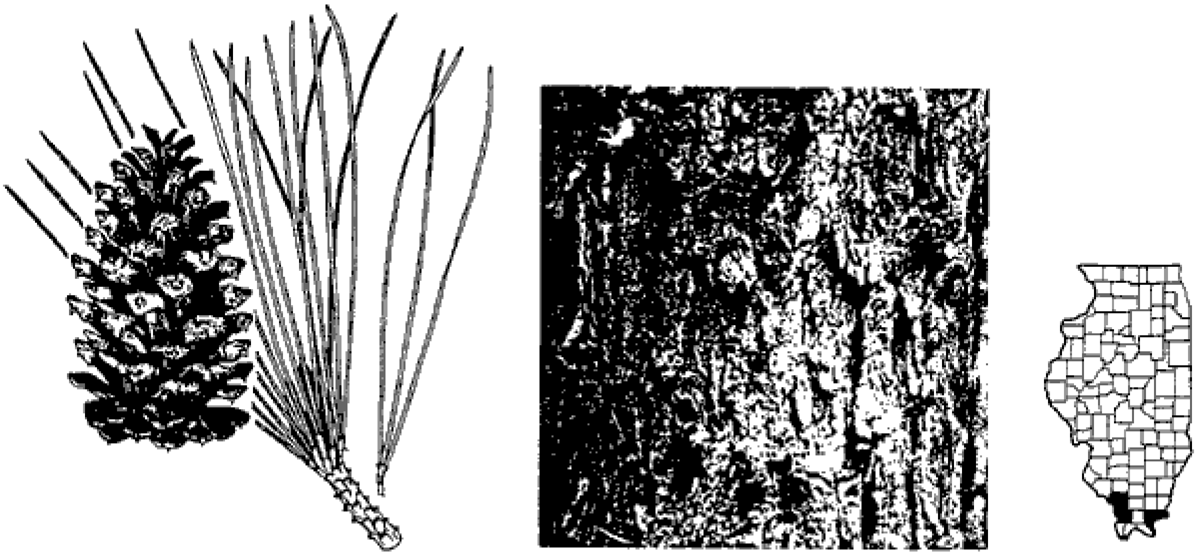
Prevention

- Suspend lumbering operations when bred cattle are present. The latter part of gestation seems to be the dangerous period, although some evidence suggests that the early part of gestation seems to be the dangerous period and simply goes unreported.
- Keep pregnant cows off ranges that include ponderosa pine trees.

Loblolly Pine - *Pinus taeda L.*

Other Name - Old-field Pine.
Growth Form - Large tree sometimes over 125 feet tall; trunk diameter up to 2 feet; crown rounded.
Bark - Reddish-brown, divided into irregular plates.
Twigs - Slender, brown, becoming roughened.
Leaves - Needles in clusters of 3 or occasionally 2, stiff, up to 9 inches long, light green.
Flowers - Staminate crowded into several yellow spikes up to 1/2 inch long; pistillate crowded into 1 to several

yellow clusters.
Fruit - Cones ovoid to oblong, mostly straight, up to 6 inches long, each scale compromising the cone with a short, sharp prickle; seeds rounded, up to 1/4 inch long, with a wing up to 1 inch long.
Wood - Weak, brittle, coarse-grained, yellow-brown.
Uses - Pulpwood, construction.
Habitat - Planted in plantations in Illinois, rarely escaped.
Range - New Jersey to Tennessee, south across Arkansas to eastern Texas, east to central Florida; not native in Illinois.
Distinguishing Features - The Loblolly Pine is distinguished by its stiff, long needles usually in clusters of 3 and by its long cones. It is similar to Shortleaf Pine but has longer needles and cones.



Loblolly pine (*Pinus taeda*)

Broomweed (*Gutierrezia Microcephala = Xanthocephalum* spp.)

G. microcephala - Broomweed, perennial snakeweed, slinkweed, turpentineweed.
G. sarothrae

Major Species	Usual Time of Abortion	Other Considerations	Full Table for Abortion Inducing Toxicants
Cattle, swine	After 7 to 117 days of feeding	Abortion of weak and small young	

Synonym - *Xanthocephalum* spp.

Family - Compositae

Description

- Densely branched, perennial, resinous shrub.
- Up to 2 feet tall.
- Main stems woody, leafless below, with numerous herbaceous, leafy branches above.
- Branches are ascending, ridged.
- Leaves are numerous, alternate, linear, narrow, 1 - 3 mm wide and 3/4 - 2 inches long.
- Early in growing season - bright green and aromatic late in season, is tan to grey-brown.
- Flowers are in very small composite heads, 5 - 7 mm in diameter, produced singly or in clusters at tips of numerous branchlets, especially at the upper periphery of the plant.
- Rays are yellow, with 4 or 5 per head; there are 1 - 3 disc flowers per head.

Habitat

Dry range and desert from Texas to California, north to Colorado and Idaho, south to Mexico. Its presence indicates improper grazing practices.

Toxic Principle

- Oxygenated flavonol methyl esters and diterpenoid acids have been implicated recently as the toxic agents responsible for the reproductive effects of *Gutierrezia*.
- Saponins extracted from this plant and injected have caused signs and lesions similar to those associated with ingestion; including abortion.

Susceptible Species

- Sheep, cattle, goats, swine and rabbits.
- In 1988, annual losses to the livestock industry in Texas and New Mexico due to this plant were estimated at 40 million/year.

Toxicity

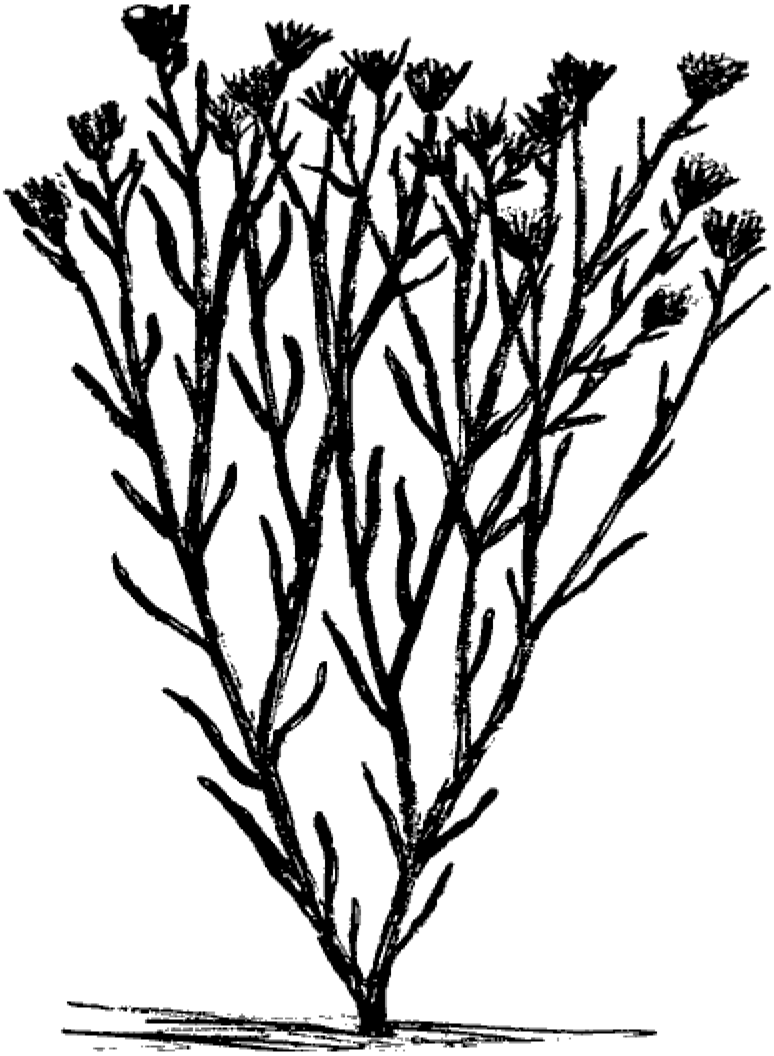
More of a problem when actively growing on sandy soils. Poisoning usually when overgrazing has forced animals to eat *Gutierrezia*.

Signs

- Abortion documented in cattle, swine and rabbits. In cattle, abortion may occur as early as 7 days or after 117 days of feeding.
- Calves may be born early and therefore underweight with poor survival rates.
- Retained placentas frequently occur.
- Occasionally the placenta is passed in part, but the calf is retained.
- Cows sometimes die.
- Low level exposure may cause vulvar swelling and premature udder development.
- In swine, abortion is the most sensitive sign. Natural cases have occurred in pastures dense with *Gutierrezia*.
- Animals with acute toxicosis (less often seen) may develop nasal discharge, listlessness, anorexia, rough coat, diarrhea or constipation.
- Mucus in feces may be observed in addition to vaginal discharge, hematuria and death. Crusting and sloughing of nasal mucosa on occasion.

Lesions

- Gastroenteritis, mild to severe.
- Hydropic degeneration and necrosis in the liver, icterus.
- Toxic nephrosis and necrosis in kidneys.
- Uterine edema, hydrops of fetal membranes in some cases.



Gutierrezia sarothrae

Cupressus Macrocarpa - Monterey Cypress

Major Species	Usual Time of Abortion	Other Considerations	Full Table for Abortion Inducing Toxicants
Cattle	2 - 8 weeks before term	Premature births, stillbirth	

Synonym - Macrocarpa

Distribution

Problems reported in Monterey peninsula of California and New Zealand.

Toxic Principle

Isocupressic acid.

Susceptible Species

Cattle.

Signs

- Premature births, stillbirths and abortions 2 - 8 weeks prior to term.
- Severe straining, weakness, ataxia, death.
- Maternal cotyledons enlarged with fetal membranes firmly adhered to them.
- Retained placentas.

Management

- Antihistamines (promethazine HCl) to reduce cotyledonary swelling.
- Avoid access to cut cypress foliage.

Juniperus communis - Juniper

Synonyms - Juniper, Cedar

Distribution

Some junipers are high elevation plants (e.g., *J. communis*) whereas others are widespread.

Susceptible Species

Presumably cattle and sheep.

Signs

Abortion and retained placenta are likely in poisoned dams, but poisoning is only poorly documented despite the high concentration of isocupressic acid in some junipers.

Management

Avoid exposure.

Iva augustifolia - Sumpweed

Major Species	Usual Time of Abortion	Other Considerations	Full Table for Abortion Inducing Toxicants
Cattle	Third trimester	Abortion; possible early mammary gland development	

Synonyms - Narrowleaf sumpweed, marshelder sumpweed

Description

- Height - Up to 1.2 m tall.
- Leaves - Lanceolate, are opposite below and alternate above; 2 - 8 mm wide and 2 - 4 cm long.
- Flowers - Heads are inconspicuous.

Habitat

- Reported to be a problem in the western United States.
- In moist, disturbed areas.

Toxicity

Seedling stage appears to be most hazardous. Signs may be seen after several weeks of ingestion.

Susceptible Species

Reported in cattle.

Signs

- **Abortion** in the last half of gestation.
- Precocious mammary development and in some cases milk production occurs.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Abortion Inducing Toxicants
Subterranean clover (*Trifolium subterranean*) (See Estrogenic Toxicants)	Cattle	Third trimester	Abortion; possible early mammary gland development	
Locoweed (*Astragalus*)	(See Toxicants that Cause Mixed Effects on the CNS)			
Lupine (*Lupinus*)	(See Toxicants with Nicotinic Effects)			
Hybrid Sudan (*Sorghum* spp.)	(See Toxicants that Cause Paralysis, and Methemoglobin Producers)			
Lead	(See Toxicants with Mixed Effects on the Central Nervous System)			
Nitrate	(See Methemoglobin Producers)			
Carbon Monoxide	(See Toxicants that Inhibit the Function of Respiratory Pigments)			
Corticosteroids	-			
Phenothiazine	(See Toxicants that Cause Skin Damage by Primary Photosensitization)			
Halogenated dioxins and related compounds; includes highly chlorinated naphtalene	(See Other Organic Compounds)			
Vitamin A-D injectable	-			
Vitamin E and Selenium (MuSe)	-			

- Subterranean clover (*Trifolium*) (See Estrogenic Toxicants)
- Locoweed (*Astragalus*) (See Toxicants that Cause Mixed Effects on the CNS)
- Lupine (*Lupinus*) (See Toxicants with Nicotinic Effects)
- Hybrid Sudan (*Sorghum* spp.) (See Toxicants that Cause Paralysis and Methemoglobin Producers)
- *Nitrate (See Methemoglobin Producers)
- Carbon Monoxide (See Toxicants that Inhibit the Function of Respiratory Pigments)
- Corticosteroids
- Halogenated Dioxins and Related Compounds, Includes Highly Chlorinated Naphthalene (See Other Organic Compounds)
- Lead (See Toxicants with Mixed Effects on the Central Nervous System)
- Phenothiazine (See Toxicants that Cause Skin Damage by Primary Photosensitization)

Estrogenic and Anti-androgenic Toxicants

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Mycotoxicoses Introduction

Introduction

The word mycotoxin is derived from myco, meaning mold and toxin, a poison. A great number of mold metabolites have been identified as mycotoxins.
Thus mycotoxins are secondary fungal metabolites (i.e., metabolites not essential to the normal growth and reproduction of the fungus) which cause pathologic, physiologic, and/or biochemical lesions in other species (may include animals, plants, other microbes, etc.).

Mycotoxicosis - Poisoning of a biological system by a mycotoxin.
Conditions predisposing to mycotoxin production (not just trichothecenes):

1. **Moisture**:

   Field fungi - Invade developing and mature seed grain while still on the plant. The optimal moisture content for growth is 22% - 25%.
   Storage fungi - Invade seed grain after harvest while in storage. Optimal moisture for growth is 13% - 18%.
   Advanced decay fungi - Generally require moisture of 22% - 25% but rarely develop and grow on seed grain in the field.

2. **Temperature**:

   Generally molds grow readily between 20 ºC and 30 ºC. But optimal temperature ranges are from below 0 ºC to above 60 ºC. Temperature variations affect the growth rate of the mold and also the type and amount of toxins produced.

3. **Aeration**:

   Molds are aerobic organisms, but a significant difference in oxygen requirements exist between types of molds.

4. **Substrate Availability**:

   Molds can either be parasitic or saprophytic in nutrient requirements.

5. **Host Stress**:

   Important for field fungi. Environmental stress, insect damage, and plant disease encourage colonization, growth, and toxin production by fungi.

Many factors contribute to the occurrence of mycotoxicoses in livestock. For example, modern harvesting methods in which corn is handled at higher moisture concentrations combined with damage occurring in harvesting machinery increases the number of kernels in which molds can get started. Also the feeding of ground rations prevents the animals from sorting out and avoiding damaged kernels.

A Partial Listing of the Known Mycotoxins

- Related mycotoxins: Aflatoxins B_1, B_2, G_1, G_2, M_1, M_2, Q_1, and aflatoxicol.
    - Sterigmatocystins

    - Versicolorins
    - Aspertoxins
    - Autocystins
    - Sterigmatin
    - Bipolarin
    - Averufarin
    - Curvularin
- Rubratoxins A and B - Hepatotoxic
- Sporodesmin - Hepatoxic
- Penicillic acid - Hepatoxic
- Ochratoxin series, especially ochratoxin A - Nephrotoxic, carcinogenic, immunosuppressive
- Citrinin
- Citreoviridin
- Luteoskyrin
- Ergot alkaloids
    - Ergotamine
    - Ergonovine
    - Others
- Tremorgens
    - Penitrem A
    - Roquefortine
    - Paspaline
    - Paspalanine
    - Paspalitrems A and B
    - Verruculogen
    - Fumitremorgen
    - Fumigaclavine
- Slaframine
- Patulin
- Fusarium toxins
    - Trichothecenes
        - T-2 toxin
        - Diacetoxyscirpenol (DAS)
        - Deoxynivalenol (Vomitoxin) (DON)
        - Verrucarins
        - Roridins
        - Satratoxins
        - (30+ others)
    - Zearalenone and zearalenol
    - Butenolide
    - Moniliformin
    - Fusaric acid
    - Fusarin A-D
    - Unidentified refusal factors
    - Fumonisins
- Our present knowledge of many of these and numerous other known mycotoxins is extremely limited. In many instances, no surveys of the frequencies of occurrence have been done. In other instances, the compounds have been investigated in some detail but surveys have not revealed sufficiently frequent occurrence in the United States for these toxins to be of major concern to veterinarians. For example, T-2 toxin and diacetoxyscirpenol have been studied in some detail but are only rarely encountered in the United States. T-2 toxin, however, was apparently responsible for severe outbreaks of mycotoxicosis in humans and animals in the Soviet Union and has caused occasional outbreaks of toxicosis in the midwestern USA and Canada. Similarly the nephrotoxic mycotoxin, ochratoxin A, although not often a major problem in the USA, has caused severe problems in poultry in the US, occasional problems in swine in the US, and widespread outbreaks of toxicosis in swine in Denmark.
- For the present, 4 mycotoxins account for at least 95% of the confirmed diagnoses of mycotoxicoses in the midwestern USA. These toxins include the fumonisins, deoxynivalenol (vomitoxin), zearalenone, and aflatoxins.
- When extremely high concentrations of these mycotoxins are present, interpretation of the significance of residues in feeds is straightforward.

- However, when low concentrations are present in feeds, the interpretation of the toxicologic significance of mycotoxin residues can be more difficult. This is because experimental mycotoxicoses cannot always be extrapolated directly to the field situation.

Reasons why Experimental and Field Cases of Mycotoxin Poisoning are not Identical

- Experimental mycotoxin administration.
    - Only 1 purified toxin is usually administered.
    - The diet is usually balanced and contains undamaged grains.
    - The toxin is evenly mixed in the diet.
    - The toxin concentration is known.
    - The sample is presented to the laboratory without additional mold growth or toxin production occurring.
    - A controlled environment is provided for experimental animals.
- Naturally occurring mycotoxin poisoning.
    - The identified toxin is consumed along with related mold metabolites and possibly other unidentified mycotoxins.
    - Mold damaged, stressed grains may be of lower nutrient value and altered palatability.
    - The toxin(s) is (are) unevenly distributed in the diet.
    - The concentration(s) is (are) generally so variable that **multiple** samples are required to estimate concentration(s) present.
    - If sufficient moisture and appropriate temperatures occur during transit, additional mold growth and toxin production may occur.
    - Stresses such as infectious agents, reproduction, lactation, crowding, temperature variation, etc., overlap and interact with effects of mycotoxins.

Mycotoxicoses

Mycotoxicoses can occur in 3 categories: **1)** acute, **2)** subacute or chronic and **3)** subclinical with predisposition to nutritional and/or infectious disorders. Most mycotoxins cause syndromes of all 3 types. Zearalenone toxicoses, however, tend to fall into only the second category.

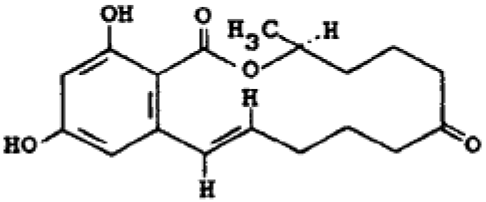
Zearalenone and Zearalenol

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Estrogenic and Anti-androgenic Toxicants
Swine, cattle, sheep	Days to weeks	Days to weeks, permanent reproductive damage rare	

Introduction

- **Zearalenone**

    This estrogen-like toxin and its relatives such as zearalenol cause subacute poisoning, as a rule, but do not cause death losses, and probably do not greatly predispose to either nutritional or infectious disorders. Zearalenone and its derivatives are the only known mycotoxins whose effects are primarily estrogenic in nature and swine are among the most sensitive domestic animals to this toxin. A 3-dimensional model of the zearalenone molecule can be used to demonstrate the similar configuration of this toxin to estradiol. As a result, zearalenone can occupy and stimulate estrogenic receptors.



Zearalenone

- **Zearalenol**

  α-Zearalenol is associated with natural zearalenone occurrence and may have 3 times the estrogenic activity of zearalenone. It is not, however, routinely included in mycotoxin screens by analytical laboratories. Although zearalenone and α-zearalenol may occur as products of other species of *Fusarium* and may coexist with T-2 toxin and other mycotoxins, they are produced primarily by *F. roseum* and coexist (as far as we know at present) primarily with deoxynivalenol (vomitoxin). In the field, estrogenic effects may occur in swine fed rations in which only a few parts per million of zearalenone are present. In these instances the diagnosis is usually confirmed when normal reproductive function occurs after withdrawal of the contaminated feed. Of course efforts to rule out infectious agents, in the case of infertility and/or abortion should not await the results of mycotoxin assays. In swine, estrogens are luteotropic and would be expected to maintain pregnancy.

Sources

- Zearalenone is produced by species of *Fusarium*, primarily *F. roseum*.
  - Corn, wheat, other grains, and occasionally forages may be contaminated by zearalenone.
  - Very high concentrations up to approximately 20 ppm have been found in 1996 wheat.

Susceptible Species

Swine, cattle, sheep; whereas chickens appear to be largely resistant.

Effects of Zearalenone

- Swine (most susceptible).
  - In prepubertal gilts.
    - Swelling and edema of vulva.
    - Vaginal and rectal prolapse.
    - Uterine enlargement, edema.
    - Atrophy of ovaries.
    - Enlargement of mammary glands.
    - Thin catarrhal exudate from vulva.
    - Differential diagnosis-normal estrus, injury to external genitalia.
  - In young boars.
    - Atrophy of testes.
    - Zearalenone in prepubertal boars may reduce libido and plasma testosterone.
  - In castrated or prepubertal males.
    - Enlargement of mammary glands.
    - May see preputial enlargement.
  - In sows.
    - Anestrus or nymphomania dependent on stage of animal's estrous cycle when first exposed.
    - Reduced litter size due to fetal resorption (mummification) and/or implantation failure when dietary zearalenone is present at 7 - 10 days postmating.
    - Weak or stillborn pigs. Piglets occasionally exhibit swollen vulvas at or shortly after birth (juvenile hyperestrogenism) whether this is from exposure *in utero* and/or through the dam's milk is currently under investigation.

        - Pseudopregnancy.
        - Field observations of zearalenone-caused abortions are now thought to be largely erroneous since estrogens are luteotropic in swine. Instead, it is suspected that implantation failure followed by pseudopregnancy leads to a diagnosis of abortion. Other etiologies (different mycotoxins, viruses, etc.) should be considered to more likely to account for most late-term abortions.
    - Differential diagnoses.
        - Pseudorabies.
        - Leptospirosis.
        - Enterovirus.
        - Parvovirus.
        - Encephalomyocarditis (EMC) virus.
        - Other mycotoxins.
- Cattle.
    - In cattle, ruminal metabolism may alter toxicity; may be associated with precocious udder development in heifers and reduced fertility in breeding animals.
    - Most animals exposed to zearalenone for brief periods of time will probably recover normal reproductive function. However, at least in females, severe toxicosis may be characterized by ovarian fibrosis and changes in the oviduct and uterus which could conceivably have more prolonged effects on reproduction. Further study of this area is needed.
- Sheep.
    - Decrease in ovulation rate and lambing percentage.
    - *Fusarium* spp. growing on pasture is a recognized cause of exposure to estrogenic mycotoxins in New Zealand.

Diagnosis

- Zearalenone and zearalenol can be quantified by high performance liquid chromatography in feedstuffs at most veterinary diagnostic laboratories. Also request zearalenone glycoside.
- Second choice screening tests include Neogen's Veratox, Agriscreen ®.
    - ELISA test (used to screen feeds) for zearalenone.

Management

- Recent research has suggested that permanent reproductive damage rarely occurs. Once animals are on clean feed and have excreted the zearalenone, normal reproductive function should occur.
- Recovery should occur in 7 - 10 days, although more time may be required for sows to start cycling. However, culling sows **may** be more economical than waiting for a return to a normal reproductive cycle.
- Recent studies indicate that zearalenone is extensively recycled through the enterohepatic system. Therefore, intestinal binding agents (activated charcoal, bentonite clays) or agents that decrease GI transit time (e.g., alfalfa fiber) may enhance elimination and decrease the time needed for animals to regain normal function.
- Other mycotoxins have been associated with reproductive abnormalities (experimental evidence). Also, interactions of mycotoxins must be considered in field conditions.

Trifolium (Clovers) and *Medicago* (Alfalfa and Medics)

Trifolium hybridum - Alsike clover

T. incarnatum - Crimson clover

T. pratense - Red clover

T. repens - White clover

T. subterraneum - Subclover, subterranean clover

Medicago sativa - Alfalfa

***Medicago* spp.** - Barrel Medic

M. denticulata (M. hispida) - Bur clover

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Estrogenic and Anti-androgenic Toxicants
Sheep and possible cattle	Chronic	With prolonged exposure, can have permanent infertility	

Family - Leguminosae (pulse or bean family)

Habitat

- Strains of clover and alfalfa are cultivated in pastures or for hay, in sandy and more fertile soils.
- *T. hybridum* - United States and Canada.
- *T. incarnatum* - Central Eastern States.
- *T. pratense* - Missouri, Illinois, Indiana, Ohio.
- *T. repens* - Europe, New Zealand.
- *T. subterraneum* - Pacific Northwest; Australia.
- *M. sativa* - United States and Canada.
- *M. denticulata* - Greatest abundance in California and Cotton Belt.

Description/General

- Plant - Tufted or diffuse herb.
- Leaves - Palmate (sometimes pinnate), 3 foliolate; leaflets, toothed; stipules united with the petiole.
- Flowers - In heads or spikes; calyx-5 cleft, corolla mostly withering or persistent.
- Fruit - Small membranous pods often included in calyx; 1 - 6 seeded, indehiscent.

Toxic Principles; Absorption, Distribution, Metabolism and Excretion (ADME)

- *T. hybridum*
  - Unknown agent causing primary and/or secondary (hepatogenous) photosensitization.
- *T. incarnatum*.
  - Stiff wiry hairs; mechanical injury (impaction), may cause photosensitization.
- *T. pratense*.
  - May contain isoflavone estrogens including formononetin especially in spring. Estrogenicity declines after flowering.
  - May cause photosensitization.
  - When attacked by *Rhizoctonia leguminicola*, the muscarinic toxin, slaframine (causes most problems due to red clover ingestion) may be present (in the fungal elements), swainsonine also may be produced.
- *T. repens*.
  - Moderate amounts of cyanogenic glycosides.
  - When affected by foliar diseases, may produce estrogenic coumestans including coumestrol, trifoliol, and repensol.
- *T. subterraneum*.
  - Genistein, formononetin, and biochanin A are isoflavone estrogens causes most if not all the problems associated with subterranean clover. Formononetin is low in estrogenic activity and is converted to the estrogenic metabolite, equol. The fresh plant and rapidly dried hay retain the isoflavone estrogens. The scenescent plant loses estrogenicity.
- *M. sativa*.
  - Coumestan estrogens including coumestrol, 4-methoxycoumestrol and sativol.
  - Estrogenic compounds are potentially produced in larger concentrations in response to damage by aphids or fungi.
  - Strains of alfalfa, fertilizer, humidity, and age of the plant may also influence estrogenicity.
  - Saponins (cause bloat).
  - Unknown agent may cause photosensitization.
- *Medicago* spp. (annual medics).
  - Coumestrol and 4-methoxycoumestrol.

Susceptible Species

- *T. hybridum* (Alsike clover).
  - Horses seem most sensitive.
- *T. incarnatum* (Crimson clover).
  - Horses are primarily affected (impaction with phytobezoars).
- *T. pratense* (Red clover).
  - Cattle, horses, sheep are all susceptible to slaframine.
- *T. repens* (White clover).
  - May contain cyanogenic glycosides but cyanide toxicosis is quite unlikely.
  - Ergot-like effects reported in other countries as were paresis in newborn pigs from spinal cord demyelination.
- *T. subterraneum* (Subterranean clover).
  - Sheep are mainly affected. Cattle are less sensitive and may excrete phytoestrogens faster than sheep.
- *Medicago* spp. (Alfalfa, medics, bur clover).
  - Excellent forage plant but may cause bloat in ruminants; estrogenic effects are less frequently encountered and occur primarily in ruminants.

Mechanisms of Action, Signs and Lesions

- *T. hybridum* (Alsike clover).
  - Syndrome I (especially horse).
    - Nervous and digestive disorders.
    - Photosensitization: "Trifoliosis" is characterized by reddening of the skin as a response to sunlight, superficial or deep dry necrosis of the skin or edematous swelling and serous discharge from the affected area. Sometimes called "Dew poisoning": moist areas of the body are most susceptible.
    - Painful irritation and shallow ulceration of oral mucous membranes and the tongue.
    - Colic, diarrhea, depressed or excited.
    - If stomatitis is severe, horses will not eat and develop dermatitis.
  - Syndrome II.
    - Recurring attacks of severe icterus.
    - Severe emaciation, sluggishness, anorexia, unsteadiness, depression, eventual stupor, manic walking, urine dark colored.
    - "Big Liver Disease" - Liver pale and rubbery.
- *T. incarnatum* (Crimson clover).
  - Colic and/or death due to impaction with phytobezoars.
- *T. pratense* (Red clover).
  - The effects of slaframine are discussed in a previous handout.
  - May cause bloat.
  - May be estrogenic.
  - Haylage has caused infertility in female cattle.
  - Rarely may contain toxic amounts of cyanogenic glycosides or goitrogens. Also, rarely may cause hepatic necrosis and photosensitization.
- *T. repens* (White clover).
  - Refer to other handouts on cyanide and cyanogenic plants or on ergot alkaloids, depending upon the syndrome observed.
- *T. subterraneum* (Subterranean clover).
  - Formononetin causes cystic glandular hyperplasia of the cervix. The cervical mucosa may resemble that of the uterus. Ewes are most prone to this effect.
    - Increases in amount and fluidity of cervical mucus causing poor sperm penetration to the oviduct.
    - Increased loss of fertilized embryos.
    - Hydrops uteri, uterine infections and reduced milk production.
    - Infertility may persist after animals are removed from pasture and has been called permanent.
- Males
  - Coumestrins and formononetrin.
    - Rams - Fertility unaffected.

        - Wethers - Develop enlarged teats, with occasional lactation (clear or milky). Increased mortality with animals on these pastures, associated with urinary obstruction.
- *Medicago sativa* (Alfalfa).
    - Coumestrin - Induced infertility is generally regarded as temporary.
    - Coumesterol of alfalfa causes decreased fertility by decreasing the rate of transport of ova in the oviduct (thought to be reversible upon cessation of exposure). Most phytoestrogens are a problem in green plants except coumesterol (in *Medicago* spp).
    - Saponins may cause bloat.

Diagnosis

- Identification of *Trifolium* or *Medicago*, evidence of sufficient consumption and appropriate clinical signs.
- **Note** - Infertility often may arise without outward signs of estrogenicity. However, histologic lesions of the cervix are an important diagnostic criterion, especially in ewes.

Treatment

- Remove from source of plant.
- For photosensitization, keep indoors for 5 - 7 days or until sensitivity passes.

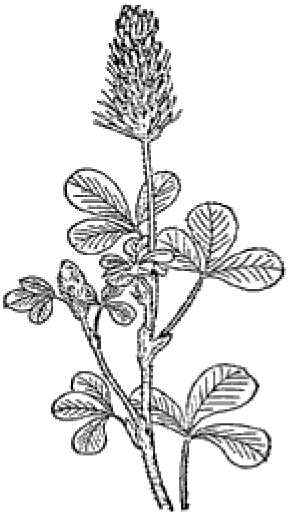


Fig. Crimson clover (*Trifolium incarnatum*). (U.S. Dept. Agr.).

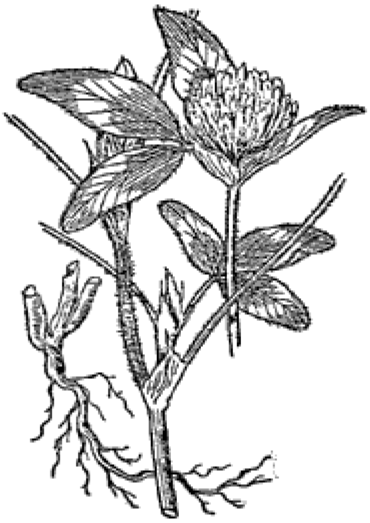


Fig. Red clover (*Trifolium pratense*). (U.S. Dept. Agr.).

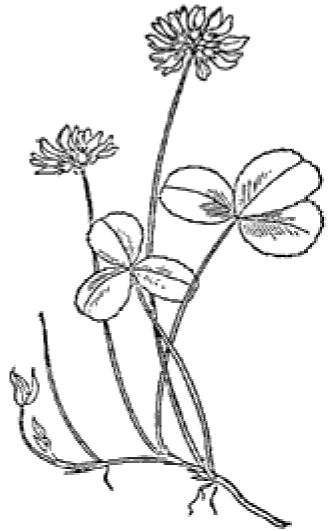


Fig. White clover (*Trifolium repens*). (Lamson-Scribner, U.S. Dept. Agr.).

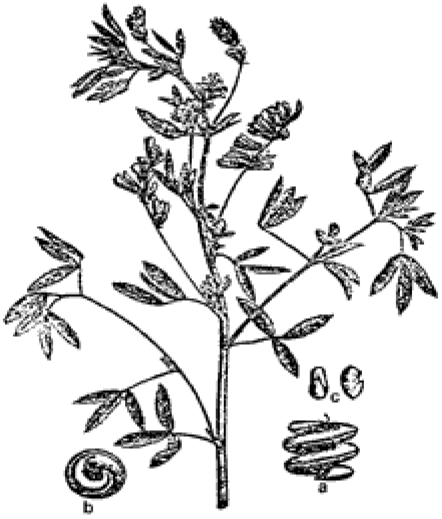


Fig. Alfalfa (*Medicago sativa*). a, b, seed pod; c, seed. (U.S. Dept. Agr.).

Alsike Clover (*Trifolium hybridum* L.)

Family - Pea (Leguminosae).
Growth Form - Perennial herb.
Stems - Upright, smooth or nearly so, branched, up to 2 feet tall.
Leaves - Alternate, divided into 3 leaflets, the leaflets obovate, rounded at the tip, tapering to the base, toothed, smooth, up to 1 inch long.
Flower Arrangement - Many flowers, crowded together into spherical heads, each head borne on a long stalk.
Flowers - Pink or pinkish white, about 1/3 inch long, borne on very short stalks.
Sepals - 5, green, united below.
Petals - 5, pink or pinkish white, arranged to form a typical pea-shaped flower.
Stamens - 10.
Pistils - Overy superior.
Fruits - Pods elongated, with 2 - 4 seeds.
Habitat - Open, disturbed soils.
Range - Throughout the state.
Time of Flowering - June to September.
Note - The scientific name of *hybridum* comes from the fact that this species appears to be an intermediate between white clover and red clover.

Black Medic (*Medicago lupulina* L.)

Family - Pea (Leguminosae).
Growth Form - Annual herb from fibrous roots.
Stems - Spreading, branched, hairy, up to 18 inches long.
Leaves - Alternate, divided into 3 leaflets, the leaflets oval to obovate, rounded at the tip, tapering or rounded at the base, toothed, hairy, about 1/2 inch long.
Flower Arrangement - Several flowers crowded together into dense heads 1/2 to 3/4 inch long, the head borne on a stalk.
Flowers - Yellow, about 1/12 inch long.
Sepals - 5, green, united below.
Petals - 5, yellow, arranged to form a typical pea-shaped flower.
Stamens - 10.
Pistils - Ovary superior.
Fruits - Pods spirally curved, smooth, black, 1-seeded.
Habitat - Open ground, in fields and along roads.
Range - Throughout the state.
Time of Flowering - May-July.

Other Estrogenic Toxicants

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Estrogenic and Anti-androgenic Toxicants
Diethylstillbesterol (**DES**) (no longer available)	All species	Hours to days	Once used in dogs for mismating and urinary incontinence. Transplacental carcinogen in women exposed *in utero*	
ECP (**estradiol cypionate**)	Dogs	Hours to days	Weeks to months; potentially lethal	
Wheat germ	-	-	-	
Soybean (*Glycine max*)	-	-	-	

Diethylstilbestrol (DES)

- Used in dogs - Urinary incontinence, mismating.

- Mechanism of action of estrogens (as abortifacients), change oviduct or uterine environment, alleviation of transit time through uterine tubes, or inhibition of implantation.
- Carcinogenic.
    - Related to higher incidence of breast cancer in women (chronic exposure).
    - Adenocarcinoma of the vagina in female offspring of women treated with DES early in pregnancy (transplacental carcinogenesis).
    - Methods are available to detect DES residues in meat (DES use as a growth promotant in cattle was banned years ago).
    - Possible cause of bone marrow suppression (rare).

Estradiol Cypionate (ECP)

- ECP is the oil-soluble 17 β-cyclopropylpropionate ester of alpha estradiol.
- Used for mismating treatment in dogs.
- ECP, estrone, estradiol benzoate may cause bone marrow depression and aplastic anemic. Estrogens may also cause cystic ovaries and uterine abnormalities.
- Administration of ECP during diestrus has been associated with increased incidence of endometrial hyperplasia and pyometra.

Wheat Germ

Estrogenic, but relationship to clinical estrogenic effects not established.

Soybeans, Tofu, Other Soy-Based Foods

Genistein, glycitin, and daidzen in soybeans are comparatively weak isoflavone estrogens that, by competing for natural estrogens, are associated epidemiologically with a decrease in the incidence of breast cancer in women. Also, in elderly women, the estrogens seem to decrease osteoporosis.

DDT and Metabolites: Reproductive Effects and Effects on the Adrenal Gland

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Estrogenic and Anti-androgenic Toxicants
Estrogenic Compounds				
DDT and DDE	-	-	-	
Some PCBs (See Organic Compounds that Affect the Skin)	-	-	-	
Anti-androgenic Toxicants				
p,p'-DDT, and especially p,p'-DDE	-	-	-	
Some PCBs (See Organic Compounds that Affect the Skin)	-	-	-	

Adrenal Effects

Another contaminant of DDT and a lesser metabolite in DDT metabolism, o,p'DDD causes damage to the adrenal cortex of dogs. A resulting decrease in response to ACTH occurs. As a result of this property, o,p'DDD is used in primary hyperadrenocorticism of dogs in a pharmaceutical preparation, (generic also called mitotane) and the brand name Lysodren. Excessive or prolonged therapy with this drug may result in excessive damage to the adrenal cortex and Addisonian crisis.

Reproductive Effects

o,p'DDT, a contaminant of technical grade DDT is more estrogenic than p,p'DDT which makes up the bulk of the formulation. The feminizing effects of DDT are now thought to be due primarily to the anti-androgenic effects of p,p'DDE. Feminization is related to effects of DDT derivatives at hormone receptors rather than to an ovarian response.

Note - p,p'DDE associated feminization is believed to account for an epidemic of feminization in alligators in parts of Florida. p,p'DDE is the principal environmental degradation product of DDT.

DDT is also known to cause induction of thin eggshells in raptors. Because of the lipophilicity of DDT and its metabolites, the agents accumulate in the lipids of living organisms, especially in aquatic systems. As a result, aquatic predators such as bald eagles were among the most severely affected. There may also be another problem, which has been hypothesized to be due to enzyme induction and resultant enhanced metabolism of estrogens. Delayed estrus; fewer eggs layed; and some young born too late to be ready to leave for the fall migration may result.

Other Organochlorines

Dieldrin, endosulfan and some PCB have estrogenic properties. Dieldrin, endosulfan, and presumably others may exhibit marked synergism with regard to estrogenic effects.

Estrogen-induced Pancytopenia in the Ferret

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Estrogenic and Anti-androgenic Toxicants
Estrogenic Compounds				
Endogenous estrogen-induced pancytopenia in the ferret	Ferrets	Any unmated female ferret	Months; very often lethal	

Source

The female European ferret (*Mustela outorius*) is an induced ovulator. Female ferrets usually reach sexual maturity at 8 months of age. The onset of estrus is indicated by pronounced vulvar swellng. Unbred females may remain in heat for long periods of time (up to 1 year). The prolonged presence of elevated blood estrogen levels results in bone marrow supression and pancytopenia.

Clinical Signs

Often present as lethargic, with a history of having been in heat for an extended period of time (months). Affected females are from 8 months to 7 years of age. Physical exam reveals pale mucous membranes, and ecchymotic or petechial hemorrhage of the oral mucosa and subcutis. A systolic murmur, weak rapid femoral pulse, dyspnea, hypothermia, and dark mucoid stool may be noticed. Weight loss is a constant finding (normal average adult female weight 680 grams, rectal temperature 102.0, heart rate 216 - 242/minute). Partial or complete alopecia may be present.

Clinical Pathology

Parameter		Normal	Pancytopenia
PCV (%)		35.0 - 51.0	4.0 - 17.0
TP (gm/dl)		5.8 - 7.4	5.5 - 12.0
Platelets (/µl)		68,000 - 500,000	33,000 - 420,000
WBC (/µ)		9,000 - 13,000	2,000 - 6,900

RBC X 10^6 /µl	9.98	1.2 - 3.0	

Treatment

- Supportive treatment for hypothermia and dehydration is often required for a successful outcome. IV fluid therapy should be started (tranquilization or anesthesia may be required; ketamine hydrochloride 10 - 30 mg/kg IM or SQ may be given). IV administration of corticosteroids may be required for shock. Transfusion therapy if PCV is below 10% is ideal (jugular is preferred site for collection from donor ferret).
- Therapy of choice for estrus termination is via administration of human chorionic gonadotropin or ovariohysterectomy after stabilization of clotting parameters and restoration of a near normal blood profile. Postoperative hypothermia may occur and should be avoided. A high calorie, vitamin-mineral enriched diet may be required in the immediate postoperative period.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Estrogenic and Anti-androgenic Toxicants
Nonylphenol Plasticizer and component of some detergents and a surfactant used in pesticides; pollution may feminize aquatic animals, possibly terrestrial animals as well				

Section IX: Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation

Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation

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North American Poisonous Snakes

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
All species	Minutes to hours	Several hours to days; potentially lethal	

Clinical Signs - Snake Bites - General

- Snakebite is not always easy to diagnose. The presence of a heavy haircoat and local swelling obscures fang marks. One or more fang puncture wounds may be present on the animal. The most common locations for fang marks in small animals are the face and legs. Horses are commonly bitten in the nose, head, and neck. Bites to the legs of horses are less common and may present with minimal swelling.
- If venom is directly injected into the blood stream, severe systemic signs and sometimes rapid death occur.

Crotalidae - Pit vipers, all have deep pit between eye and nostril. All pit vipers and a few nonpoisonous snakes have vertically elliptical pupils. Pit viper fangs are hollow and retractable, located near the front of the maxilla. The body of pit vipers is distinctly narrower than the back of the head giving them a more "arrow-like" shape than most other snakes.

Agkistrodon - Moccasins, copperheads
A. piscivorus - Cottonmouth moccasin
A. contortrix - Southern copperhead
Adults may attain length of 3.5 feet (average 2.5 feet). Dark forms have dumbbell, hourglass, or crossband figures of reddish brown or chestnut color. Head is generally lighter color than rest of body.
Crotalus - Rattlesnakes
C. horridus - Timber rattlesnake
C. willardi - Ridgenosed rattlesnake
C. adamanteus - Eastern diamondback rattlesnake
C. horridus atricaudatus - Canebrake rattlesnake
Adult C. horridus may attain lenght of 6 feet (average 3 feet). Occur in dark and light color phases, latter often confused with "diamondback". All rattlesnakes have rattle.
Sistrurus - Pygmy rattlesnake
S. catenatus - Massasaupas
Adults can reach 3 feet in length (average 22 - 30 inches). Have rattle, general body color is brown to gray.

Toxic Principle

- Pit viper venoms (rattlesnakes, cottonmouth, and copperhead) are primarily necrotizing and hemolyzing; however, other body systems can be involved. Venoms primarily contain enzymatic and proteinaceous toxins. Phospholipase A is a strong hemolytic, myotoxic agent that contributes to cardiotoxicity. L-amino-oxidase and other homologous enzymes may be responsible for the activation of tissue peptidases. Hyaluronidase (spreading factor) may enhance tissue penetration. Proteases are implicated in the anticoagulation events. Nonenzymatic polypeptides are also present, e.g., hemorrhagins, cardiotoxin, neurotoxin. Hemorrhagins in crotalid venom are vasculotoxic causing rapid hemorrhage and edema at the wound site, in addition to systemic hemorrhage and shock.

- In all cases the severity of the bite depends on the location and amount of toxin injected, the size of the animal bitten, and the specific toxicity of the venom. Copperheads (*A. contortrix*) are considered the least toxic, the Mojave rattlesnake (*C. scutulatus*) the most lethal, and the appressive Eastern rattlesnake (*C. adamenteus*) the most likely to envenomate its victim. The amount (if any) of venom injected is regulated by the snake. In Crotalidae up to 20% of bites do not result in envenomation.
- Depth of venom penetration is dependent on the length of the snake's fangs and the presence of "spreading factors".
- Behavioral differences between snakes exists, e.g., aggressiveness.
- Mortality in horses bitten by rattlesnakes has been reported at 10 - 30%. Often occurs 5 - 7 days past envenomation due to secondary complications, e.g., myopathy, hepatopathy.
- Major route of venom excretion is the kidneys. Variable amounts of biotransformation occur.

Crotalidae Clinical Signs

- When venom (pit viper) is injected into the tissues, pain, erythema, and edema develop as a result of the activation of bradykinins, histamine, and other inflammatory mediators. Swelling may become extensive and may be accompanied by petechia, ecchymosis, and hematomas.
- In general, crotalid venoms produce alterations in resistance (decrease in arterial pressure) and loss of integrity of blood vessels. Changes in the integrity of blood coagulation mechanisms often occur. In part, these are thought to be due to a thrombin-like enzyme, which acts directly on fibrinogen with subsequent abnormal clotting (Note - In general no change in PT or in the activity of factors VII, X, or XII occurs). DIC may occur.
- If signs of erythema and edema do not occur within 20 minutes, envenomation has probably not occurred; however, it is possible in a minority of cases to have systemic signs without local involvement.
- Systemic signs (dogs) are noted as the clinical course continues, these include hypotension with tachycardia, pulmonary edema, salivation, diarrhea, renal failure, and shock. Cardiac arrhythmias include premature ventricular contractions and ventricular tachycardia have been commonly reported. After a few hours hemolytic anemia often develops. In advanced cases, lethargy and paralysis develop. Death is due to respiratory and circulatory collapse.
- If strikes occur in the head and neck region, local swelling with secondary respiratory distress may be noted.
- Clinical signs in horses include initial excitement, anxiety, and pain. May act colicky. Lameness in all animals may be an early clinical sign.
- Clinical pathology changes: anemia can be profound due to hemolysis and extravasation.

Elapidae - Cobra family. The only North American representative is the coral snake (*Micrurus euryxanthus*). Distribution limited to southeast and southwestern USA. Small pair of fangs in the cranial maxilla; 20 - 44 inches in length; tend to be nonaggressive, reclusive. Snakes have to "chew" on prey in order to envenomate. Have bright rings of red and white or yellow, red and yellow bands touch. In nonvenomous snakes the yellow rings are separated on each side by a black ring. Nemonic device: "Red on yellow, *kill a fellow*; red on black, *venom-lack*".

Coral snake venom is primarily neurotoxic (due to a neurotoxic polypeptide). Cholinesterase activity is present in the venom of some species; however, this is not thought to be the major neurotoxic principle.

Elapidae Clinical Signs

Coral snake venom causes local pain and swelling. Within a half hour neurotoxic effects may be noted. Clinical signs in dogs receiving sublethal doses are lethargy, tremors, incoordination, and occasional hematuria. Lethal doses are associated with vomiting, salivation, defecation, generalized parasympathetic stimulation, followed by respiratory paralysis and death. Pharyngeal paralysis can result in aspiration pneumonia.

Therapy - Snake Bite - General

- Snake bite is an urgent emergency. In some cases, it is lethal, in many it can cause prolonged and disfiguring injury. Although the animal should receive veterinary care as soon as possible, this should be done while keeping the animal as quiet as possible.

- Even if the snake is killed for identification purposes, caution must be exercised in handling it after death. Envenomation is possible even after a poisonous snake has been decapitated.
- Objectives of therapy are: neutralize the venom, prevent shock, and prevent secondary infections; and sometimes to prevent the further spread of toxins, and remove the venom. The use of alcohol to clean the wound is contraindicated because of its vasodilatory effect, which would promote uptake and spread of venom.
- Crotalidae Antivenins:
    - Human and canine antivenin is available (Antivenin [crotalidae] - Polyvalent - Dodge Laboratories and Wyeth Laboratories). The manufacturer's recommended dose for dogs is 10 - 50 ml IV (check label for current recommendations). Actual dose, frequency, and duration of administration should depend on alleviation of clinical signs including swelling, pain, shock, etc. Dogs treated within 60 minutes of receiving lethal doses of venom showed increased survival rates. The effectiveness of antivenoms is greatest if administered within 4 hours of the bite. Has variable effectiveness at preventing necrosis. The use of antivenom in humans and domestic animals has been associated with severe anaphylactic reactions (serum sickness). Pretreatment with diphenhydramine is recommended. Epinephrine should be available.
    - Canine
        - Usually one bottle of antivenin is given, but 2 or 3 are sometimes needed.
        - Antivenin can be mixed in fluids.
        - Start with 5 ml over a 5-minute period. Monitor the inside of the pinna for hyperemia and the animal's overall appearance for any other evidence of a potential allergic reaction. If there is no reaction, the administration should continue. Antihistamines (such as diphenhydramine) may be used to offset allergic reactions. For anaphylactic reactions, the treatment should also include corticosteroids and epinephrine.
    - Horse
        - Usually 1 to 4 bottles of antivenin are used.
        - Watch carefully for allergic reactions including anaphylaxis and treat as indicated (see above).
- Coral Snake Antivenin:
    - Wyeth also manufactures an antivenin for coral snake bites. Keep in mind that signs may be delayed and that responses to antivenin may sometimes be poor after signs are present. Usually 2 vials of antivenin may be given IV before the onset of clinical signs. Start with a low dose and handle apparent allergic reactions as for crotalid antivenin above.
- Antibiotics: The prophylactic use of antibiotics is indicated. Broad spectrum antibiotics are commonly chosen.
- Respiratory assistance (ventilator) may be needed for 48 - 72 hours for animals with coral snake poisoning.
- Fluid therapy: Generally indicated in small animals. Hypotension is a common presenting sign. Maintain diuresis to facilitate excretion, renal damage has been reported in man.
- Corticosteroids: Use is controversial. Useful in treating shock but increases in mortality have been reported with their use. They can also alter results of laboratory tests that are otherwise useful in monitoring an animal's progress. Generally used for prevention of shock and hypotension. May not affect local swelling.
- Transfusions: Commonly indicated in dogs, if necessary, to treat anemia and hemorrhage.
- Supportive: The maintenance of a patent airway is critical. Large diameter tubing or opened syringe cases are commonly placed in the nostrils of horses bitten on the face to keep the airways open. Emergency tracheostomy may be required. Tranquilization in horses may be required.
- Tetanus antitoxin should **always** be given to the horse.

Therapies Generally Contraindicated

- Tourniquet - The use of tourniquets is controversial and usually they are avoided. When used they are most effective in first 30 minutes. Tourniquets increase local tissue damage due to hypoxia. The general location of snake bites (e.g., face) may prevent use. Recommended **only** for animals in which the tissues below the tourniquet will be sacrificed to save the animal's life!
- Incision and suction - Also controversial. Requires restraint of animal to be effective. Minimal benefit with regards to the local removal of venom. Not recommended unless pocket of venom will clearly be removable. Do **not** make cruciate incisions. They increase necrosis of the skin.
- Cryotherapy - Commonly associated with increased tissue damage. **Not** recommended.

- Surgical debridement - Use has not been substantiated. May result in serious scarring and loss of function. May not prevent systemic signs. **Not** recommended early in course of treatment for envenomation.

Brown Recluse Spider or Fiddle Back (*Loxosceles reclusa*)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
All species	Minutes to hours	Days to months; rarely lethal; rarely recognized toxicosis	

Description

Medium size, brown, on the dorsal surface most have a violin-shaped mark with the handle directed posteriorly.

Toxic Principle

Proteins include protease, hyaluronidase, sphingomyelinase D, and esterase. Have direct lytic effect on RBCs.

Signs

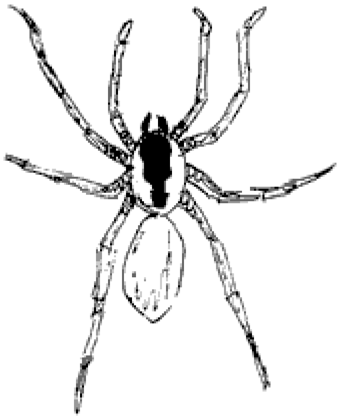
- The bite initially stings, then 1 of 2 forms may take place. The cutaneous form begins as edema, progresses to an ulcerated wound. The viscerocutaneous form, which is severe, produces hemolytic anemia, hemoglobinuria, icterus and hyperthermia.
- Ninety percent of the cases heal in 1 - 3 weeks. Some may need skin grafting.

Mechanism

- Unidentified venom component is cytotoxic to endothelial cells. Triggers intravascular coagulation and microthrombi formation within capillaries. Capillary occlusion, hemorrhage, and necrosis occur.
- Polymononuclear leukocytes and complement play important roles in potentiating the response to envenomation.

Treatment

- Steroids may be used to protect against systemic effects. Manage hemolytic anemia if needed by use of fluids and bicarbonate to minimize hemoglobin deposition in renal tubules and by blood transfusion if anemia is severe enough to justify.
- Early surgical excision or corticosteroids were not effective in experimental rabbit based models of loxoscelism. Allowing ulcerated areas to granulate is acceptable management.
- The leukocyte inhibitor, dapsone, was effective in reducing inflammation at the site of brown recluse venom injection.



Loxosceles reclusa

Brown Recluse Spider - Two to four cm leg span. Color range: yellow-tan to dark brown. Has 6 eyes (most spiders have 8 eyes). Violin-shaped marking extending from eyes to abdomen.

Ergot Alkaloids and Gangrenous Ergotism (Saint Anthony's Fire)

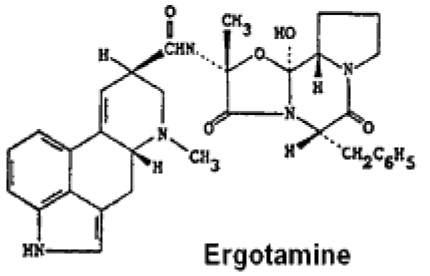
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
Cattle sheep	Days to weeks	Weeks; potentially lethal	

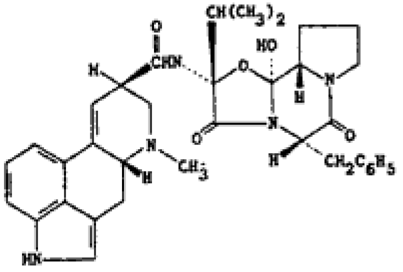
Sources

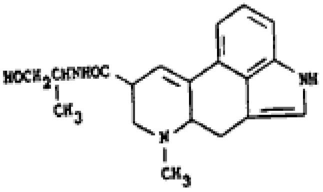
- The term ergot is used in 2 ways: **1**) as the common name for the fungus *Claviceps* which invades the ovary of grasses and cereals and **2**) used to refer to the sclerotium, the hard purple mass of mycelium hyphae that replaces the heads of grasses.
- In the midwest, *C. purpurea* is the most common fungus invading grasses. The host plant range includes: rye, triticale, barley, oats, brome grass, timothy and quack grasses.
- In commercial grain trade, wheat or rye are classified as "ergoty" if more than .3% by weight are comprised of ergot sclerotia and oats, triticale or barley are so graded when they contain more than .1%.
- In some parts of the world, *Claviceps* fungi have been isolated from sorghum grain that contained ergot alkaloids.
- Ergot poisoning, sometimes of epidemic proportions has occurred in persons due to the ingestion of smutted rye. Toxic amounts were associated with abortifacient effects and this effect led to its use to hasten labor. Unfortunately, this use led to excessive uterine contraction frequently and often caused ischemic damage to the child. In the present use of ergot alkaloids, the only rational objective is to prevent postpartum bleeding.

Toxic Principle

- The toxic action of ergot is due to the numerous alkaloids (ergotamine, ergocristine, ergonovine, etc.) present in the sclerotia and other components-choline, ACH, histamine, sterols. Over 40 alkaloids have been identified which are derivatives of lysergic acid, some of which are inactive.
- The important naturally occurring alkaloids are ergotamine and ergonovine. Of these, ergonovine is more readily absorbed. Both compounds are potent smooth muscle activators. LSD is also derived from ergot, and the smooth muscle contracting activity, although sometimes present, is not always seen. LSD causes depersonalization or hallucinations and may produce toxic psychosis.


Ergotamine


Ergocristine


Ergonovine

Absorption, Distribution, Metabolism and Excretion (ADME)

- Metabolism (detoxification) of the ergot alkaloids is assumed to take place in the liver, since toxic effects are more likely in persons with liver dysfunction.
- Meat and milk residues have not been detected in any field outbreaks.

Mechanism of Action

- The wide spectrum of pharmacological activity is attributed in part to the alkaloids' agonist/antagonist activity at alpha adrenoreceptors, 5-HT receptors and dopamine receptors. The primary effects are central/ neurohormonal and peripheral. The peripheral effects include an oxytocic-like effect on the uterus and vasoconstriction from smooth muscle contraction.
- The central neurohormonal effect mimics the effects of dopamine. Dopaminergic action may result in a reduction in prolactin which can adversely affect (reduce) milk production.
- All smooth muscles, vascular and nonvascular, are contracted, and there is no dependence on innervation or any other chemical mediators.
- Only at term is uterine muscle more sensitive to ergot than is other smooth muscle. Therefore in early pregnancy, ergot cannot be used as an abortifacient. Furthermore in early pregnancy, these alkaloids are more stimulatory to the cervix, than to the uterus. Ergot is not recommended in any context as an abortifacient. For the induction of labor, oxytocin is very much preferred.
- The blood vessels in all vascular beds are constricted by the ergot alkaloids, but the larger arteries are most sensitive. Occlusion may occur, as shown by arteriograms. The result is ischemia of the tissues perfused by the artery. It is possible for blood flow to be reestablished without permanent damage, or the tissue may become gangrenous before the process reverses. The limbs, toes, ears and tail are often affected, but usually not all in the same animal.

Toxicity

Animal responses vary with the total and individual alkaloid content, quantity of ergot in the feed, frequency of ingestion, climatic conditions (cool, wet weather) and animal species. All domestic animals, birds and man are susceptible. In human medicine, the gangrenous reaction sometimes occurs at therapeutic doses, although it occurs more often with excessive doses.

Signs

- Ergot poisoning is commonly seen in cattle. Clinical signs include: reduced feed intake, unthriftiness, **lameness**, swelling and sloughing of feet below the fetlocks (generally the hind feet). Usually a line of demarcation separates the proximal viable tissue and the distal dry cold epidermis. Less commonly the ears and tail are sloughed.
- Affected extremities may become inflamed and then cold, with numbness and dry gangrene developing. Eventually, there is a painless loss of tissue. The gangrenous form results when animals ingest ergot alkaloids over periods of days or weeks.
- Other clinical signs may include poor milk production, nervous signs, and reduced conception.
- The primary signs in swine with ergotism are **agalactia**, early parturition, weak or dead pigs, infertility and **reduced rate of gain**.
- In sheep, necrosis of the tongue, gastroenteritis, abortions, gangrene and central nervous system involvement are reported.

Diagnosis

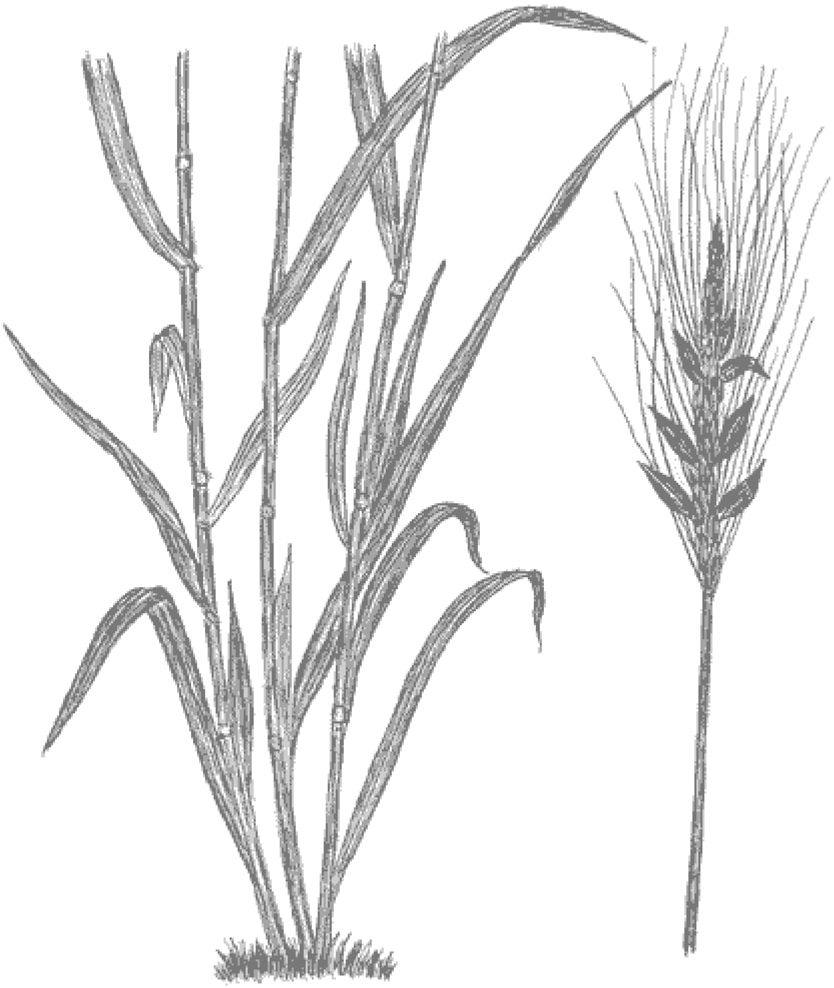
- Ingestion of ergoty small grains (ergot does **not** occur in corn).
- Ergot alkaloids in grains may be identified in toxicology laboratories by gas chromatography-mass spectrometry or less sophisticated methods including thin-layer and high pressure liquid chromatography.

Treatment

- Isolate from source.
- Control secondary bacterial infections.
- Move animals to a dry, warm environment.
- Keeping the animals warm is indicated to avoid the added insult of lower environmental temperature to the vascular insult. In warm weather, fly control is essential.
- Of several drugs and maneuvers tried to alleviate the vasoconstriction, only nitroprusside infusions showed any promise.

Prevention

- Control of ergot - Climatic conditions are involved in yearly incidence.
- Mow grasses prior to flowering.



Ergot - Note the ergot structures extruding from the seed heads of barley (right). These structures replace the normal grain and are the toxic stage in the life cycle of ergot.

Festuca Arundinacea - Tall Fescue

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
Cattle	Weeks to months	Weeks to months	

Description

- Coarse perennial grass, deeply rooted, in vigorous clumps, reaching 3 - 4 feet in height when mature.
- Leaves broad, dark-green, ribbed, and rough on the upper surfaces.
- Inflorescence paniculate, nodding, to 1 foot in length
- Spikelets many-flowered.

Habitat

Tall fescue is a major forage grass,grown on an estimated 35 million acres and will tolerate being closely grazed. The grass is sometimes allowed to "accumulate or stockpile" for winter grazing. Fescue is sometimes cultivated as hay. Fescue is especially important in the transition area of the USA between North and South.

Toxic Principle

- The toxic principles are apparently produced by the endophytic (inside the grass) fungus, *Neotyphodium coenophialum*, previously known as *Acremonium coenophianum*; and before that, *Epichloe typhina*. This fungus is a *Clavicipitaceae fungus* which is transmitted in the seed (and not via spores) and can, produce ergot alkaloids. Ergovaline is the ergot alkaloid of greatest significance in endophyte-infected fescue. It is estimated that over 90% of tall fescue fields in the United States are infected with the endophyte to some extent, with an average of 62% of the plants infected within each field.
- Pyrrolizidine alkaloids including N-acetylloline, N-formylloline, and dimethyl-N-acetylloline have been isolated from Kentucky fescue. Also, the alkaloid perloline has been identified in endophyte-infected fescue. However, the significance of these types of alkaloids remains to be demonstrated.

Mechanisms of Action

Ergovaline is believed to account for the decrease in prolactin, and other effects of endophyte-infected fescue, most of which are compatible with the effect of ergot alkaloids (gangrene and low milk production, for example).

Signs

- The syndromes associated with tall fescue include:
    - Summer syndrome in cattle.
    - Fescue foot in cattle.
    - Fat necrosis in cattle.
    - Reproductive and lactation problems in cattle, horses and sheep
- Cattle.
    - **Summer syndrome**:
    - Poor weight gain, reduced feed intake
    - Reduced conception rates
    - Intolerance to heat
    - Failure to shed the winter hair coat (rough hair)
    - Elevated body temperature
    - Nervousness, excessive salivation

    - More prevalent where fescue is present as a monoculture and where high nitrogen fertilization is used.
- **Fescue foot:**
    - Some fescue fields have a history of repeated fescue foot outbreaks, but in general, the outbreaks are non-recurring. Conditions which favor the fescue foot syndrome include the feeding of the fall regrowth or the total yearly accumulated fescue (longer stockpiling increases incidence).
    - Lameness most often occurs with the onset of cooler or cold weather (below 60 ºF and especially with snow or ice).
    - Cattle on low-quality rations, and underweight are predisposed, animals in good flesh are not immune.
    - Onset is 5 - 15 days, up to weeks after on pasture, occasionally where continuously pastured.
    - Slight arching of the back.
    - Rough hair coat.
    - Soreness in 1 or both rear limbs, weight shifting, holding 1 foot up.
    - Knuckling.
    - Loose stools.
    - Reddening of the coronary band, then swelling.
    - Redness, swelling and then purple-black discoloration of the tail.
    - Sloughing of the ear tips.
    - Sloughing of the feet, usually at or just above the coronary band, sometimes, higher.
    - **Fat necrosis**:
    - Lipomatosis or fat necrosis is defined as the presence of masses of hard or necrotic fat in the adipose tissue of the abdominal cavity.
    - Affected fat has yellowish or chalky white irregular masses of very hard fat, especially in the mesenteries.
    - These may be detected on rectal exam. Subcutaneous fat is not affected.
    - Digestive disturbances, due to obstruction or intestinal constriction, scanty feces, bloating and occassionally death occur.
    - Dystocia due to hardening of fat around the birth canal may occur also.
    - Similarly urine retention has been encountered secondary to these fat deposits with associated postrenal uremia.
    - Other signs associated with fat necrosis include; weight loss, poor appetite, listlessness and rough hair coat.
    - Predisposing factors include the presence of fescue in monoculture and heavy nitrogen fertilization.
- Horse, sheep, cattle.
    - Predisposition to laminitis in horses has also been associated with exposure to endophyte-infected fescue.
    - **Reproductive and lactation problems** in cattle, horses and sheep: The primary problems are abortion, weak to stillborn young and moderate to severe agalactia. The effects result in the death of many neonates.
        - Cattle.
            - Typically a farmer with cows on a problem pasture will have a 70 - 80% calf crop, which is made worse by fertilization, but improves with the addition of clover to the pasture. Dairy cows may have a marked decrease in milk production. Prolactin concentrations are depressed in cows ingesting affected fescue.
        - Horses.
            - Horses may abort or more often have dystocia after a prolonged gestation, and may have a thick placenta that increases the need for human assistance during parturition. Serum cortisol concentrations did not increase normally near parturition in mares grazing a problem fescue pasture, and serum prolactin levels were extremely low. The low milk production may be attributable to the low prolactin levels. Prolactin is responsible for the initiation and maintenance of lactation and possibly for the initiation and maintenance of the corpus luteum as well. The decrease in prolactin may therefore also be responsible for the early abortion and fetal resorption in affected species, but this remains to be verified.
            - Predisposition to laminitis in horses has also been associated with exposure to endophyte-infected fescue.

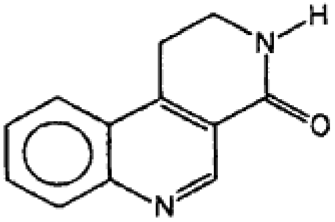
- Ewes.
    - Serum prolactin levels are depressed by ingestion of affected fescue.
    - Increased rate of return to estrus.

Treatment of Fescue Foot

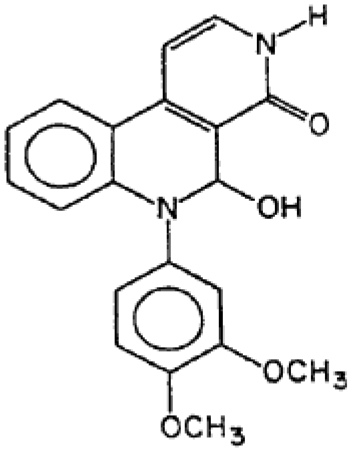
- Remove from fescue pasture, when 1st signs occur.
- Rule out foot rot, frost bite, mechanical injuries such as stone bruising.

Management

- Mix legumes and other grasses with the fescue stand or supplement the diet with other feeds. This appears to work well with cattle but apparently dystocia in pregnant mares may occur with as little as 5 - 10% of the ground cover in a pasture as infected fescue.
- Rotational grazing.
- Do not fertilize with over 200 lb of nitrogen per acre per year.
- Feeding hay may lessen problems; field cured fescue hay, processed in the early dough to boot stage, when quality is at a maximum is considered safe for feeding to cattle. However, toxic fescue cut for hay remains toxic.
- Observe cattle daily for lameness or stiffness, especially during the first month on pasture and in cold weather. Observe in early AM before cattle warm out of the lameness. Move affected animals to another field or put them on another feed.
- Calves on 1 or 2 lb of corn per day had less problems, than those getting no grain.
- Adequate protein and mineral supplementation should be assured.
- Avoid stress especially in cold weather.
- Addition of a legume to the pasture sharply increases gains. Ladino clover also improves conception rates.
- If new plantings of fescue are to be done, the use of old seed is recommended, since the fungus dies after 1 year under normal storage conditions in the lower South. New cultivars of fescue, such as Johnstone from Alabama and Triumph are relatively free of the endophyte. Some states require tags on bags of fescue seed to state the percent of endophyte infection. Strains should be chosen with 0 - 5% infection rate.



Perlolidine



Perloline

Tall fescue alkaloids - The authors are skeptical that these 2 compounds play a major role in the toxic effects of fescue.

Tall fescue, *Festuca arudinacea*.

Juglans Nigra - Black Walnut - Toxicosis in Horses

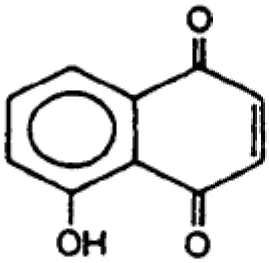
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
Horses (cause of lamintis in horses)	12 - 24 hours	Days; rarely lethal unless 3rd phalanx rotates through the sole	

Source

- Black walnut (*Juglans nigra*) is native to the eastern United States, growing in the well-drained soil of the Appalachians and midwestern valleys.
- The wood is commonly used and prized as furniture and gun barrel stocks.
- The resultant shavings and sawdust are shipped wherever a market exists.

Toxic Principle

- Preliminary investigative work in an effort to identify the causative agent in walnut shavings laminitis was focused on "juglone" (5-hydroxy-1,4-naphthaquinone), a naphthoquinine toxin found in members of the walnut and hickory family.
- Juglone is also present in other members of the walnut family (Persian or English walnuts, butternuts, hickories, and pecans).
- The structure of juglone is as follows.



Juglone

- Experimental attempts to reproduce the clinical syndrome by using juglone were less than convincing.
- Experiments administering juglone in differing concentrations orally and topically (distal metacarpus to coronary band) have inconsistently produced clinical signs but not full-blown laminitis. Intravenous administration to one horse produced acute pulmonary edema and death.
- Juglone is believed to be responsible for the poor success of other vegetation beneath black walnut trees but is **not** likely to be responsible for black walnut toxicosis of horses.

Toxicity

- Field reports indicate that laminitis has occurred when bedding contained only 5 - 20% black walnut shavings.
- All parts of the tree may be toxic including the heartwood, leaves, roots, and bark.
- Every black walnut tree does not have naturally occurring toxicity, implying environmental factors may alter the tree's toxicity.
- The toxin appears to act by causing a sensitization of vessels of the foot to the effects of adrenergic agonists such that acutely there is a reduction in the function of blood flow to the foot that reaches the dorsal laminae.

Signs

- Rapid onset, 12 - 24 hours after exposure.
- Commonly, several if not most horses of a group may be acutely affected with laminitis.
- Depression.
- Laminitis.
- Laminitic stance. Can see acute and/or chronic laminitis, and in either case, there can be rotation of P-3.
- Reluctance to move, resistance to attempts to pick up feet.
- Digital pulse evident, elevated hoof temperature in affected digits.
- Slight to moderate edema in limbs, from carpus and tarsus down.
- Increased respiratory rate and effort.
- Increased borborygmi.
- Elevated temperature and pulse.

Lesions

Necrosis of dorsal laminae followed by mitotic activity in an effort to repair the damage.

Treatment

- Remove black walnut shavings.
- Wash legs with mild soap.
- Mineral oil or activated charcoal and a saline cathartic; do not use mineral oil with a saline cathartic.

Laminitis Treatment Can Include:

- Phenylbutazone.
- Soft bedding (damp sand), or padded shoe.

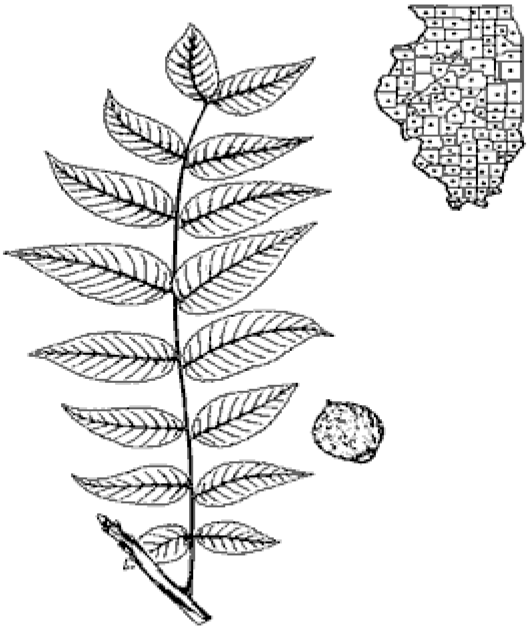
- Removal of shoes.
- Acepromazine, or a more specific alpha blocker (i.e., prazosin), to restore circulation to the dorsal laminae and possibly heparin to prevent microthrombi formation.

Prevention

Do not use fresh black walnut shavings for bedding.

Black Walnut, *Juglans nigra* L.

Growth Form - Large tree up to 150 feet tall; trunk diameter up to 5 feet; crown broadly rounded; trunk straight, columnar, not buttressed at the base.
Bark - Black, thick, deeply furrowed.
Twigs - Stout, greenish or orange-brown, hairy, smooth and gray; pith brown, divided by partitions; leaf scars alternate, shield-shaped, elevated, with 3 bundle traces.
Buds - More or less rounded at the tip, pale brown, soft, hairy, up to 1/2 inch long.
Leaves - Alternate, pinnately compounded, with 15 **-** 23 leaflets; leaflets up to 3 1/2 inches long and 1 1/2 inches wide, broadly lance-shaped, pointed at the tip, rounded at the asymmetrical base, toothed along the edges, yellow-green and smooth on the upper surface, paler and hairy on the lower surface, turning yellow in the autumn.
Flowers - Borne separately but on the same tree, appearing when the leaves are partly grown, the staminate several in thick, yellow-green, hairy catkins, the pistillate much fewer in small spikes, neither of them with petals.
Fruit - In groups of 1 or 2, spherical, up to 2 inches in diameter, green or yellow-green, slightly roughened, the husk thick, the nut very hard, oval, dark brown, deeply ridged, the seed sweet.
Wood - Hard, heavy, course-grained, dark brown.
Uses - The wood is used for furniture, interior finishing, cabinets; the nuts are edible.
Habitat - Rich woodlands.
Range - Massachusetts across to Minnesota, south to Texas, east to Florida.
Distinguishing Features - The Black Walnut is recognized by its characteristic buds, its chambered pith, and its fruits.



Berteroa Incana - Hoary Alyssum

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
Horses (leg swelling and lamintis)	1 - 2 days	Days to a week; rarely lethal	

Description

Hoary alyssum is an annual or perennial herb 30 - 90 cm tall with narrow, hairy, alternate leaves 1 - 7 cm long. Flowers are on racemes, very small and white with four deeply divided petals. Pods are hairy and approximately 0.5 cm long.

Habitat

Hoary alyssum is found in north central and northeastern United States and Canada. It grows well on overgrazed pastures, poorly managed hayfields, and waste places.

Toxic Principle

Unknown.

Susceptible Species

Horses.

Toxicity

The palatability of hoary alyssum is poor, and horses given the choice will usually ignore it in a pasture or preferentially eat another component of hay. In poor pasture or with very weedy hay, this is often not possible.

Signs

- Fever, pounding digital pulses, limb edema, and laminitis may develop within 24 hours of consumption of hay containing more than 30% hoary alyssum. Death due to hoary alyssum toxicosis has been rare to date. Only mild limb edema has been reported in horses grazing heavily infested pastures.
- Response to the plant is variable. In field cases and feeding trials, fewer than 50% of horses consuming hoary alyssum showed any clinical signs.
- Signs normally resolve within 4 - 5 days following removal of the source of hoary alyssum unless laminitis has occurred. Recovery from laminitis may be very prolonged if severe.

Lesions

Limb edema, laminitis with or without rotation of P3, petechiae and ecchymoses on serosal surfaces, and occasionally hemoperitoneum or hemothorax. Perivascular hemorrhage and hemosiderin-laden macrophages in the spleen may be seen histologically.

Diagnosis

Clinical signs, lesions, and history of exposure.

Treatment

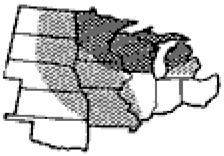
- Remove horses from infested pasture or source of hay.

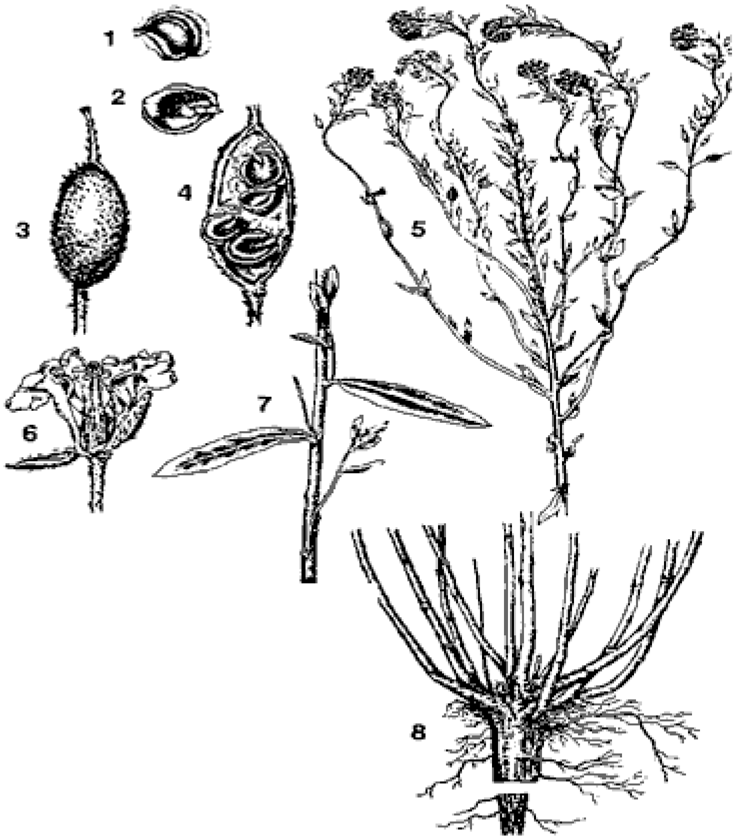
- No standard treatment protocol has been established. Consider the use of activated charcoal for recent exposure.
- Treat for laminitis (see previous section on Black Walnut).

Prevention

- Diligent weed control in pastures and hay fields.
- Inspection of hay before purchase.

Mustard family, *Cruciferae*





Hoary Alyssum, *Berteroa incana* (L.) DC. **1**,**2**, seed; **3**, seed pod; **4**, seed pod split open; **5**, upper part of flowering plant; **6**, flower; **7**, stem; **8**, lower part of plant. **Annual**, **biennial**, or **perennial**, reproducing by seeds. The name hoary indicates many rough hairs on stems, leaves, and seed pods. **Stems** gray-green, hairy, 1 to 3 feet (30 to 90 cm) tall, with many branches near the top. **Leaves** gray-green, hairy, alternate, oblong, narrow, 1/2 to 3 inches (1.3 to 7.5 cm) long, with smooth edges. **Flowers** white, with 4 deeply divided petals, produced in long raceme. **Seed pods** hairy, swollen, oblong with short beak on the end. **Seeds** oblong, rough, dull gray-brown. **Found** in meadows, pastures, and waste places. Emerges early in the year, continues to grow throughout season, producing seeds until frost.

Additional Toxicants

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation
Thallium (See Toxicants that Affect the Skin)	All species	Hours to chronic	Days to permanent damage; often lethal	

Section X: Toxicants that Affect the Liver

Introduction to the Toxicology of the Liver

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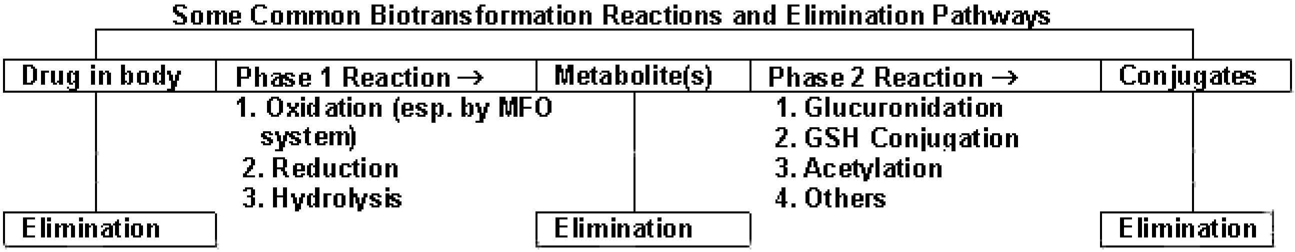
The liver is uniquely positioned as the body's primary detoxification center for ingested agents. The blood travels from the digestive tract via the portal vein directly to the liver where it percolates through the sinusoids with their porous endothelial linings. Thus, the hepatocytes are able to take up and process not only a range of nutrient substances but also many natural and manmade toxicants. In most cases, the entry of toxicants into hepatocytes is a passive process, but in some cases, such as with the water soluble algal toxins termed microcystins, active transport processes are involved in hepatocyte uptake.
Hepatic metabolism = biotransformation = usually makes xenobiotics more water soluble.

- As a result of biotransformation, more of the xenobiotic tends to be filtered by the glomerulus and less is reabsorbed by the kidney; thus, more leaves in the urine.
- Also, the metabolites tend to undergo increased active secretion by the kidney and the liver.

Some Common Biotransformation Reactions and Elimination Pathways



Processes of Metabolism are Comprised of Phase I and Phase II Reactions

- **Phase I Reactions**
  - Oxidation, reduction, hydrolysis.
    - Many oxidation and hydrolytic reactions + some reduction reactions; **many but not all** of the Phase I reactions are catalyzed by microsomal cytochrome P450 enzymes.
    - Microsomes = (laboratory altered) pieces of smooth endoplasmic reticulum.
    - P450 are membrane-bound enzymes. Therefore, substances metabolized must be somewhat lipophilic.

Some Specific Phase I Processes

A. Oxidation by P450 Enzymes

$$\text{P450} + \text{NADPH(H)} + O_2 + \text{RH} \longrightarrow \text{ROH}_2 + H_2O$$

(e$^-$ source) (substrate)*

Uses one O atom from O_2 to oxidize RH. The other O atom is reduced to H_2O. Because of these two functions of the enzyme system, it is called "mixed function oxidase".
*Substrate is often a xenobiotic, or an endogenous compound such as a hormone or fat soluble vitamin.

B. Reduction by P450 Enzymes

1. Same initial reaction
   Adds e$^-$ (electron) first as in above reaction, except here (especially if the animal is hypoxic), there is no subsequent addition of oxygen.
   Instead a reactive (often toxic) free radical is formed:

   = - R . ⟶ tissue binding ⟶ may cause liver necrosis e.g., halothane if hypoxic-increased chance of hepatotoxicity.

Normally a lot is breathed off and some is oxidatively metabolized by liver. With hypoxia →increased amount of reduction to free radical metabolites.

2. Cyclic compounds → may get addition of e- by P450 but then e- falls off → e- may hook onto oxygen to form an oxygen radical. Oxygen radicals react with lipids →lipid peroxidation (see subsequent part of this section); or e- reacts with other molecules → forms - R . (free radicals).

C. Hydrolysis as a Result of P450 Enzymatic Reactions
(Includes epoxide hydrolase)

	P450 metabolism often fast		**Epoxide hydrolase often slow**	
Cyclic compound with double bond	→	**Reactive strained epoxide which oftenreacts with macro-molecules causing cytotoxic or DNA-damaging effects**	→	**Diole (not highly toxic)**

D. Hydrolysis by Soluble Esterases
(e.g., nonspecific carboxylesterases of liver, pseudocholinesterase of blood.) (Not a P450 reaction.)

E. Oxidation by Cytosolic Enzymes
(e.g., alcohol dehydrogenase.) (Not a P450 reaction.)
Others.

Summary: Agents Affecting Mixed Function Oxidases
Induction of Cytochrome P450 Enzymes

1. Regarded by some toxicologists as a toxic effect in itself.
2. Can cause notable liver enlargement.
3. Agents that **induce** (to induce means to increase the amounts of) certain isoenzymes of **P450 can increase the toxicity of xenobiotics bioactivated by those enzymes**. For example, P450 IA enzymes are inducible by methylcholanthrene, and phenobarbital induces P450 IIB isoenzymes. Such compounds increase the toxicity of xenobiotics which are bioactivated by the specific isoenzymes that they induce. Specific examples include: aflatoxin B1, nitrosamines, bromobenzene, and carbon tetrachloride. Conversely, **if the xenobiotic is detoxified by P450** without notable activation, **induction of P450 may protect** the animal. A specific examle would be the tolerance of an animal to a drug after being on phenobarbital as an anticonvulsant. **Note** - Different P450 isoenzymes occur in different locations in the liver which can result in local activation and local damage. Generally, centrilobular areas tend to have some of the highest P450 activities overall, which can predispose to centrilobular toxic effects.
    - Inducers of microsomal enzymes, e.g., PCBs, phenobarbital, halogenated dioxin, dieldrin or other chlorinated hydrocarbon insecticides.
        - Causes an increase in liver size and weight.
        - May shorten the duration of effect of other drugs, e.g., endogenous steroids.
        - May increase susceptibility to hepatotoxic agents which act primarily after conversion to reactive metabolites by liver enzymes
          or
        - May lessen toxicity of agents whose metabolites are less toxic than parent compounds.

Inhibition of Cytochrome P450 Enzymes

Inhibitors of P450 generally do not reduce the amounts of enzyme present. They simply reduce the activity of the enzyme. If a **xenobiotic is bioactivated by P450** isoenzymes, then agents that **inhibit** the action of these

isoenzymes **protect against toxicity**.
Conversely, if a **xenobiotic is simply detoxified** by a reaction with P450 (and not activated to significant degree in the process), **inhibitors of P450 increase its toxicity**.

- Chloramphenicol is bioactivated by P450s into reactive intermediates, especially dichloroacetamido groups that acetylate and irreversibly inhibit cytochrome P450 IIB enzymes.
- Fluoroquinolone antibacterials including enrofloxacin, ciprofloxacin, and norfloxacin, inhibit cytochrome P450 IA. The inhibition is considered to be reversible.
- Macrolide antibiotics, such as erythromycin also inhibit P450s.

- Inhibitors of microsomal enzymes, e.g., chloramphenicol, piperonyl butoxide, N-octylbicycloheptene dicarboxiimide, sesame oil, and the initial (temporary) effect of inducers such as phenobarbital on the first day of dosing:
    - May prolong the effect of drugs metabolized by P450s to inactive forms.
    - May prevent liver lesions associated with agents otherwise converted by P450s in the liver to highly (locally) reactive metabolites.
    - May increase the systemic toxicity of agents which are metabolized by P450s in the liver to products less toxic than the present compound.
- **Phase II (Addition Reactions) = Conjugation Reactions** (for information on species differences see Appendix C).
    - **Glucuronidation** - Often involved and is a system with a relatively high capacity - except in cats and neonates of many species. Cats have a glucuronyl transferase, but for many xenobiotics, it is ineffective.
    - **Sulfation** - Low capacity (especially in pigs) - Other species tend to have a low amount of sulfate in pool.
    - **Conjugation Glutathione (GSH)** - Low capacity in all species but still very important in interrupting (hooking onto) highly reactive intermediates (metabolites) formed by P450 (Phase I) reactions.
    - **Amino acids** - Conjugation with various other amino acids (species dependent).
    - **Acetyl group** - Acetylation may make more or less water soluble depending upon the polarity of the original compound.
    - **Methyl group** - Methylation tends to make xenobiotics more lipid soluble; and sometimes more volatile.

Some Specific Phase II Reactions

A. Glutathione, Glutathione Conjugation, and Glutathione Depletion

Glutathione = GSH = a tripeptide composed of glycine, glutamic acid, and cysteine.
Glutathione contains a nucleophilic thiol that usually detoxifies:

1. Electrophilic carbon-containing metabolites.
2. Metabolically produced oxidizing agents. GSH tends to detoxify many reactive intermediates produced by cytochrome P450 enzymes.
3. GSH also intercepts reactive intermediates formed by spontaneous epoxide breakdown.

Glutathione-S-transferases
Conjugate GSH to numerous substrates. To be a substrate for GSH-S-transferase, the xenobiotic must:

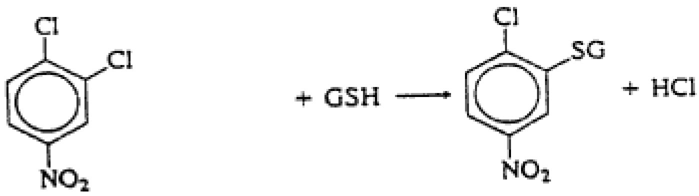
1. Be somewhat hydrophobic.
2. Contain an electrophilic carbon.
3. React nonenzymatically with GSH to some degree.

Glutathione Conjugation via Specific Glutathione-S-Transferase Reactions
Substitution Reactions (Methyl iodide)

Glutathione-S-alkyltransferase: $CH_3I + GSH \longrightarrow CH_3\text{-}SG + HI$

Glutathione-S-aryltransferase: 3,4-Dichloronitrobenzene + GSH $\longrightarrow$

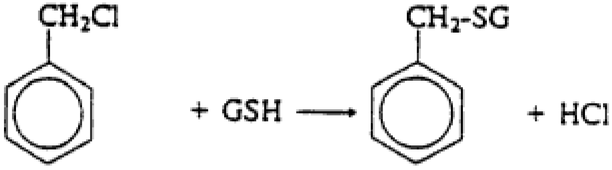
GSH loses H and 3,4-Dichloronitrobenzene loses a Cl, forming the-SG conjugate + HCl



Glutathione-S-aralkyltransferase:

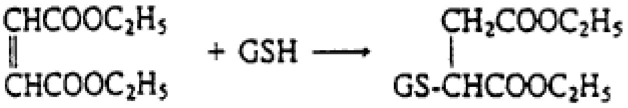
Benzyl chloride + GSH ⟶

GSH loses H and Benzyl chloride loses a Cl, forming the -SG conjugate + HCl



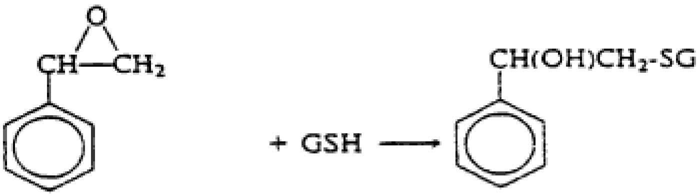
Addition Reactions

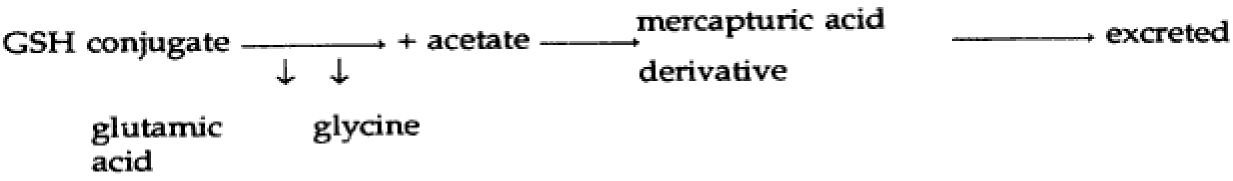
Glutathione-S-alkenetransferase: Diethyl maleate + GSH ⟶
Double bond in Diethyl maleate is broken forming the -SG conjugate on the carbon atom previously involved in the C=C bond.



$$\begin{array}{l} CHCOOC_2H_5 \\ \| \\ CHCOOC_2H_5 \end{array} + GSH \longrightarrow \begin{array}{l} CH_2COOC_2H_5 \\ | \\ GS\text{-}CHCOOC_2H_5 \end{array}$$

Glutathione-S-epoxidetransferase: 1,2 Epoxyethylbenzene + GSH ⟶ epoxide is broken and -SG conjugate is formed on carbon atom previously involved in the epoxide bond.





Further processing of GSH conjugates:

GSH conjugates are subsequently cleaved to cysteine derivatives primarily by renal enzymes and then acetylated, thus forming N-acetylcysteine derivatives (also called mercapturic acid conjugates).

GSH depletion and depletion or lack of other Phase II processes:

Examples of compounds transformed to reactive intermediates and then bound to GSH include: bromobenzene, chloroform, acetaminophen. Such toxicants may deplete GSH. Without adequate GSH

(readily depleted, low-capacity system), the reactive metabolites produced by cytochrome P450 enzymes often bind to other "vital cellular constituents" may cause local hepatotoxic or local pulmonary toxic effects. Alternatively, one compound may deplete GSH and another may be converted to a reactive, toxic intermediate.
Depletion or lack of function of other conjugation reactions (such as glucuronidation) also can predispose animals to liver (**Or Other Organ**) damage. An example includes hepatotoxicy in cats caused by phenolics.

Glutathione Peroxidase:

The enzyme reduces peroxides and lipid peroxides, for example:

GSH peroxidase*

H_2O_2 + GSH __________________⟶ H_2O

GSH peroxidase*

R-OOH + GSH________________⟶ -ROH

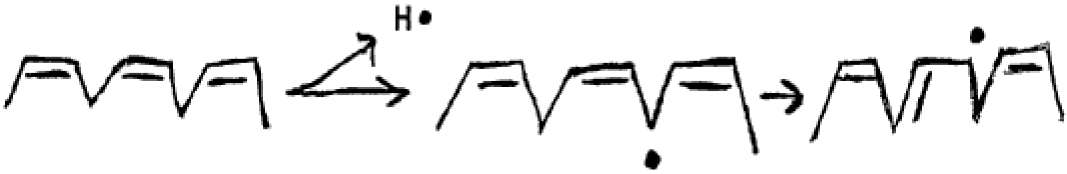
(lipid peroxide)

**normally reactive and
self-perpetuating**

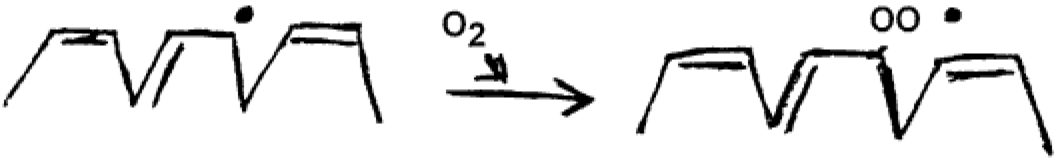
Selenium is a limiting component in glutathione peroxidase structure and thus, in its function. (This is a major reason why Se has antioxidative and anticancer effects).
GSH is a cofactor for glutathione peroxidase; and depletion of GSH can therefore diminish the body's ability to defend against lipid peroxidation (see below).

B. Lipid Peroxidation

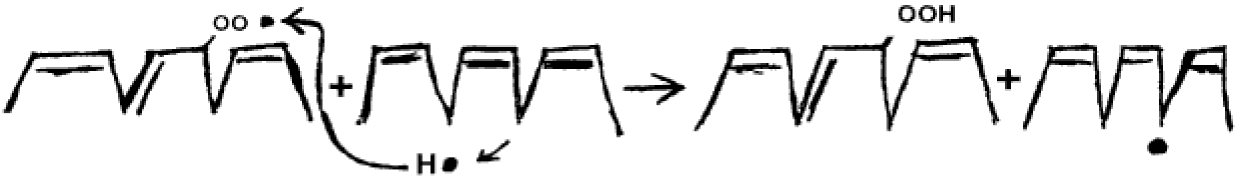
Lipid peroxidation of subcellular membranes is an important event in the pathogenesis of many toxicants. This process is believed to be important in the effects of white or yellow phosphorus and those of carbon tetrachloride on the liver and other organs.
The double bonds of polyenoic unsaturated fatty acids in the subcellular membranes are susceptible to attack by reactive chemicals (whether the compound is inherently reactive or if it is made reactive in the organism [i.e., by P450]). This attack can result in the loss of a hydrogen atom, which yields a free radical on one of the carbons of the lipid chain. This step is termed the initiation phase of lipid peroxidation.



The free radical creates instability of the lipid molecule and these undergo a series of transformations, including shifting of double bonds to form the diene configuration. Then the free radicals react with molecular oxygen to form oxygen peroxy radicals.



The peroxy radicals remove a hydrogen from a methylene group of a nearby unsaturated fatty acid, which thereby produces one hydroperoxy-lipid and a new radical.



This chain reaction is called propagation phase of lipid peroxidation; and in this process, a linear spread of lipid peroxidation occurs. The hydroperoxides are also unstable and therefore they decompose to form additional free radicals. These reactions tend to continue until they are controlled by cellular defense mechanisms or until all the available unsaturated lipids are depleted.

Due to lipid peroxidation in subcellular membranes, there is a loss in structure and function in the damaged organelles. Also, the lipid peroxides themselves and their breakdown products are toxic to the cells.

C. Disruption of Hepatic Blood Flow

Severe hepatic necrosis from any agent can cause secondary "venoocclusive" lesions (i.e., collapse of the sinusoids). Examples include acute toxicoses from: pyrrolizidine alkaloids, nitrosamines, and especially microcystins and nodularin (from blue-green algae). Ultimately, both the sinusoidal endothelium and the hepatocytes are damaged.

By contrast, some toxicants cause coagulative necrosis and the sinusoidal endothelium is spared. An example is acute carbon tetrachloride toxicosis.

Note - Some cardiotoxins and other agents that cause right sided heart failure may **indirectly** cause centrilobular necrosis because of passive congestion of the liver. This should not be confused with primary toxic hepatic injury.

D. Carcinogenesis

Liver carcinogens include (among others): aflatoxin, certain other hepatotoxic mycotoxins, some pyrrolizidine alkaloids, dialkylnitrosamines ("nitrosamines"), some organochlorine pesticides, certain PCBs, carbon tetrachloride, chloroform, and vinyl chloride. Fumonisin-containing corn (includes mutagens as well as the non-mutagenic but hepatotoxic fumonisin) causes hepatocarcinogenesis.

If there is an alteration in DNA (mutagenesis), and **if** the cell is altered so that it has cancer potential, the process is termed **initiation**. Subsequently, a change in turnover rate of cells is a common cause of **promotion**. Initiation followed by promotion can result in development of malignant tumor development (i.e., cancer).

Biotransformation of xenobiotics to reactive intermediates increases the likelihood of the formation of **adducts to DNA** (alkylation of DNA = one form of mutagenesis) or other types of DNA damage (some of which can sometimes comprise an initiation reaction). Hepatotoxicity and necrosis tends to be followed by regeneration, which increases the turnover rate (thereby causing tumor promotion).

General Appearance of Animals with Liver Failure

- Acute Liver Failure.
  - Animals may experience abdominal pain, vomiting, and hypovolemic shock if hemorrhage into liver is extensive and if it occurs over a short enough period of time. Hepatic necrosis may also contribute to shock and occasionally DIC.
  - Animals in acute liver failure may also die from hypoglycemia because of inability of the damaged liver to provide glucose.
  - Animals may also develop secondary hepatoencephalopathy from NH_3.

    - Some develop jaundice.
    - Upon palpation, liver pain and enlargement may be evident.
- Subacute Liver Failure.
    - Intermittent GI upset.
    - Appetite may be reduced.
    - Fecal color is usually reasonably normal at least initially.
    - Poor growth, production, hair coat, etc.
    - Jaundice often.
    - Possible liver pain, enlargement on palpation.
- Chronic Liver Failure.
    - Recurrent GI upset is common.
    - Chronic weight loss often occurs.
    - Hypoproteinemia may cause fluid accumulation, polyuria if severe.
    - Palpable or (more often) shrunken liver, possible cirrhosis.
    - Jaundice is variable.
    - Secondary photosensitization in some grazing animals.

Aspects of Therapy for Liver Toxicosis (General)

A. **Measures to Limit Toxicant Absorption**
B. **Measures to Support the Animal**:
    1. Fluids and antiemetics (e.g., Tigan suppositories) to avoid dehydration from vomiting, diarrhea, unwillingness to drink.
    2. Measures to alleviate shock if present.
    3. Nutritional support-frequent small feedings with low-fat, high-carbohydrate, low-volume but high-quality protein diet (to decrease workload on liver and to decrease deamination that results in formation of ammonia).
    4. Oral antibiotics to limit deamination of protein by gut bacteria.
    5. Other therapies as per liver failure.

Hepatotoxic Chemicals and Drugs

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Iron

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
Dogs, piglets, other species	Minutes to chronic	Hours to permanent damage; acute death most common in piglets	

Sources

Iron toxicosis usually results when too much iron is injected or less often when too much is give orally. Any of the iron complexes and iron salts may be involved. Baby pigs are most often involved, however, all species are potentially susceptible.

Iron From	Percent (%) Elemental Iron
Ferric phosphate	37
Ferric pyrophosphate	12
Ferrocholinate	12
Ferrous gluconate	12
Ferrous fumarate	33
Ferrous sulfate (hydrate)	20
Ferrous sulfate (dried)	37
Ferrous carbonate (anhydrous)	48
Ferroglycine sulfate	16
Peptonized iron	17

Toxicity

- Ingestion of 20 to 40 mg elemental iron/kg may result in toxicosis.
- Ingestion of ≥ 60 mg elemental iron/kg is potentially serious.
- Oral doses of iron of > 200 to 300 mg/kg is a roughly estimated lethal dose.

Mechanisms of Action

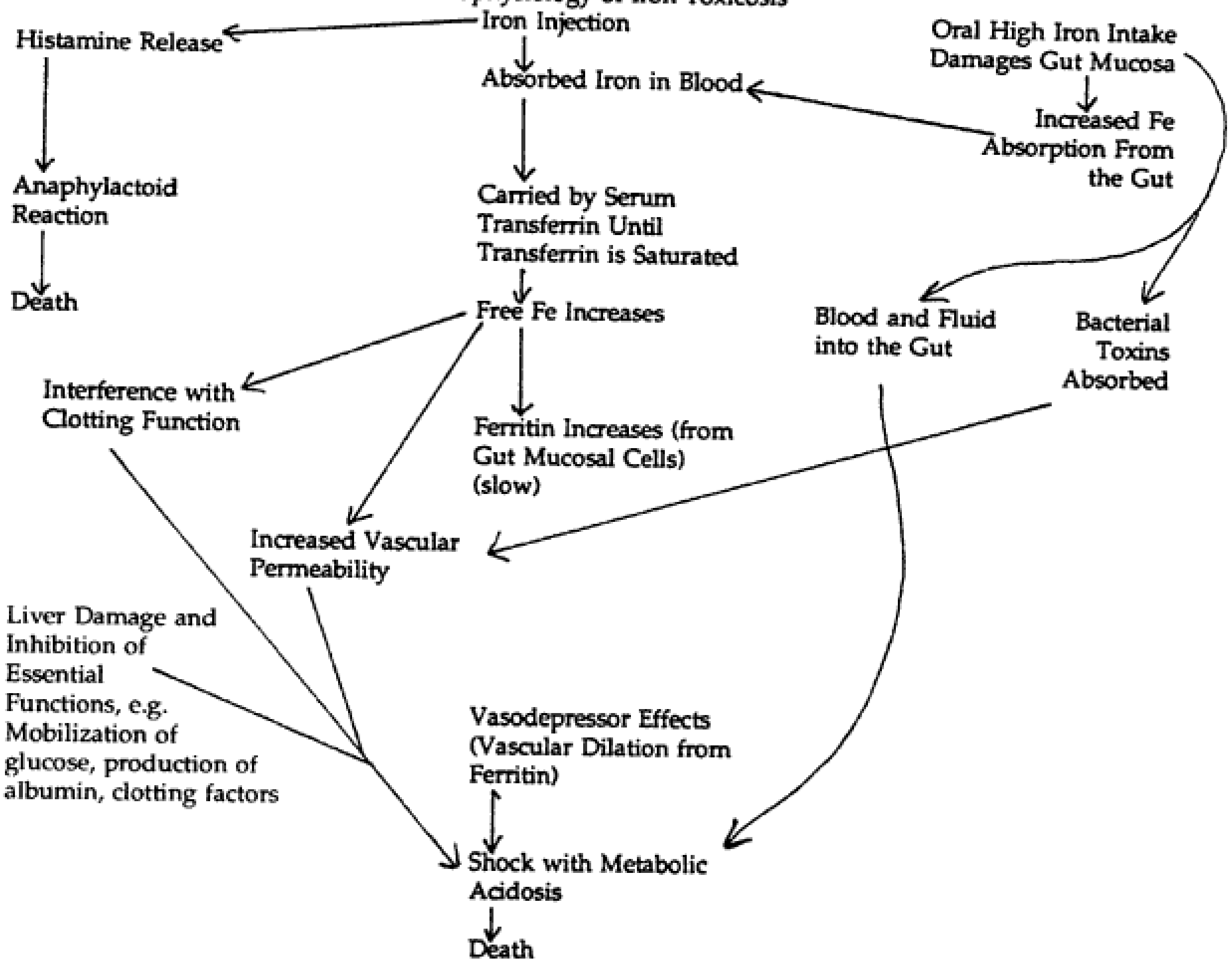
- Enhances free radical damage by superoxide radical.
- Presumably interferes with sulfhydryl groups of enzymes and other proteins.
- Direct (caustic) irritant effect on gastrointestinal tract.
- Enters the mitochondria where it acts as a mitochondrial poison, interfering with cellular respiration and resulting in metabolic acidosis.
- Two main syndromes are involved:
  - A peracute syndrome comprised of an anaphylactoid reaction. Sudden death occurs within a few minutes to hours after an iron injection.
  - Death accompanied by severe depression and coma after a subacute syndrome.
- Predisposing factors include:
  - There is no effective mechanism for excretion of iron. Therefore, animals with enough iron on board are more susceptible than those actually needing iron.
  - Pigs born to vitamin-E-selenium deficient sows are more susceptible to iron toxicosis.

- Gastrointestinal absorption of iron is controlled; however, massive doses break down the mechanism controlling absorption and toxicosis results.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Approximately 10% of dietary iron is absorbed in the ferrous (Fe^{+2}) form. In gastric and intestinal mucosal cells, iron is metabolized to the ferric state and is then transported across the cell membrane into the blood where it is bound to a $^{\beta}$-glycoprotein (transferrin) transport protein. Transferrin is normally 25 to 30% saturated in most species.
- In an acute iron overdose, the transferrin can become saturated, allowing total serum iron to exceed iron-binding capacity, increasing free circulatory iron.
- Absorption is enhanced in the presence of ascorbic acid.
- Peak absorption may occur between 1 and 6 hours after ingestion. Sustained release or enteric coated medications tend to have erratic pharmacokinetic behavior.

Pathophysiology of Iron Toxicosis


Iron Injection
Histamine Release
Anaphylactoid Reaction
Death
Absorbed Iron in Blood
Oral High Iron Intake Damages Gut Mucosa
Increased Fe Absorption From the Gut
Carried by Serum Transferrin Until Transferrin is Saturated
Free Fe Increases
Blood and Fluid into the Gut
Bacterial Toxins Absorbed
Interference with Clotting Function
Ferritin Increases (from Gut Mucosal Cells) (slow)
Increased Vascular Permeability
Liver Damage and Inhibition of Essential Functions, e.g. Mobilization of glucose, production of albumin, clotting factors
Vasodepressor Effects (Vascular Dilation from Ferritin)
Shock with Metabolic Acidosis
Death

Chronic Syndrome

Elevated iron in the diet may also cause stunting and rickets. This is a result of precipitation of phosphates in the gut as a complex with iron and has occurred at a dietary Fe concentration of 5,000 ppm.

Signs

- The peracute syndrome mimics an anaphylactic shock reaction and is primarily a vascular collapse followed by rapid death.

- In the subacute form the animal may be drowsy, may exhibit vomiting and diarrhea, both of which may be bloody, and these signs may be followed by a period of apparent improvement. Thereafter cardiovascular collapse and death occur.
- In small animals, early signs from the corrosive effect on the gut with vomiting and diarrhea develop in 0 to 6 hours postingestion. Apparent recovery may occur 6 to 24 hours postingestion followed by shock, CNS depression, GI hemorrhage, acidosis, and liver failure.
- Oliguria, anuria. Secondary to shock-induced acute renal failure.

Lesions

Lesions include a yellowish-brown discoloration and edema of the tissues, especially near the injection site. The nearby lymph nodes, and the liver and kidneys may all be dark in color. There is often edema at the injection site and subcutaneously in the injected limb. Liver damage may be apparent and histologically is characterized as periportal necrosis. After oral overdose, there may be gastric ulceration and edema.

Diagnosis

- Excessive exposure and signs and lesions are all that may be seen in the field. Iron toxicosis may occasionally occur when animals have received the recommended dose, especially if they have no deficiency to start with.
- Serum iron concentrations that correlate with the development of toxicosis (in man), e.g., human patients with serum iron concentration of > 500 $^{\mu}$g/dl (5 ppm) are considered to have serious toxicosis which requires chelation therapy. Note: serum samples drawn before 6 hours may reflect less than peak serum iron concentrations. Samples should be taken at 3, 6, 9, and 12 hours.
- Abdominal radiographs for the presence of metallic foreign bodies. Iron-containing vitamin, tablets may occasionally be apparent on abdominal radiographs.

Treatment

- Anaphylactoid reaction:
  - Antihistamines, epinephrine, oxygen, nursing care.
  - Pigs usually don't live long enough to be treated.
- Subacute:
  - Treatment is hindered by hepatic necrosis, hemorrhage and shock. Steps to enhance excretion of iron as detailed below may be worthwhile.
- Desferal ® (40 mg/kg, IM, q 4 to 8 hours), which is also known as the generic desferrioxamine or more often as deferoxamine is effective as a chelation agent to enhance the excretion of iron. One hundred mg of deferoxamine will bind approximately 9 mg of iron. Its highest affinity for iron in the ferric (+3) state. Ascorbic acid in large oral doses doubles or triples the iron excretion after deferoxamine. However, ascorbic acid should be used only **after** the gut is thoroughly cleared of iron sources. Deferoxamine must be given slowly in an IV drip (≤ 15 mg/kg/hour). When given rapidly, hypotension and shock may result. The use of deferoxamine has been documented in dogs. It is recommended when the total iron binding capacity of the serum has been exceeded. Thus, the drug is recommended when serum iron values in dogs greater than 350 $^{\mu}$g/100 ml are present; or when serum iron cannot be determined in a timely fashion and toxic doses are involved.
  - Deferoxamine challenge doses have been recommended. Deferoxamine will chelate iron, and together this causes a "vin rose" (reddish-brown) appearance to the urine.
  - Chelation therapy (in human patients) is continued until loss of urine color occurs.
- Oral exposure:
  - Early, eggs, water, milk and emetic are indicated. Lavage with a phosphate solution may be sometimes worthwhile. In children, a 1 to 1.5% sodium bicarbonate solution can be used orally to form insoluble ferrous carbonate. Experimental studies in rats suggest that oral complexation is ineffective.
  - An alternative agent to diminish the absorption of iron is milk of magnesia. The milk of magnesia (MgOH) complexes with iron to form FeOH which precipitates and is therefore not as effectively absorbed. MgOH may be of limited value in dogs.
  - Any animal in shock from iron toxicosis should also receive IV fluids and bicarbonate (may not be needed for anaphylaxis) and other appropriate supportive measures.

Prognosis

Iron toxicosis usually carries a proor prognosis.

Ferrous Fumarate Toxicosis in Foals

- In a recent outbreak of unexplained deaths in neonate foals, with deaths occurring at 2 to 5 days of age, the following clinical signs and clinical pathological findings were documented:
    - Severe depression.
    - Icterus.
    - Increased plasma NH_3.
    - Increased aromatic: branched chain amino acid ratio.
    - Increased total bilirubin in the serum.
    - Increased SGPT.
    - Increased alkaline phosphatase.
    - Increased PCV.
    - Increased partial thromboplastin time.
    - Increased prothrombin time.
    - Death.
- The cause was found to be excessive ferrous fumarate in a **Lactobacillus** preparation in a product named "Primapaste".

Lesions

Liver size was reduced to about 1/2 of normal. There was prominent bile duct proliferation which was sufficiently severe, that initially the impression was that the process had to have started *in utero*. Hepatocyte necrosis was accompanied by mild periportal fibrosis. In the brain, the presence of Alzheimer type II cells indicated the presence of hepatic encephalopathy.

Phosphorus

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
Dogs, other species	Hours to days	Days to permanent damage, often lethal	

Sources

- White or yellow forms of phosphorus are toxic and red phosphorus is not. The white or yellow types are waxy, whereas the red type is granular, insoluble and not absorbed.
- Phosphorus is occasionally used as a rodenticide and may also be encountered in electrical pastes and in incendiary and smoke bombs, used in bombing practice and warfare. The rodenticide bait is usually comprised of phosphorus mixed with grease which prevents the rapid oxidation of the phosphorus and facilitates its absorption.
- Phosphorus poisoning may result from direct ingestion of the bait or electrical paste, or from ingestion of poisoned rodents. Dermal exposure may result in burns of serious consequence.
- Accidental or malicious.

Absorption, Distribution, Metabolism and Excretion (ADME)

Phosphorus is first absorbed from the gastrointestinal tract into the blood as phosphorus but is then oxidized to phosphate. Some of the phosphorus is eliminated by the lungs which may give the exhaled air an odor of phosphorus (garlic-like) and the exhaled air may glow in the dark. Similarly vomitus or gastrointestinal tract contents may also be luminous and have the same odor.

Signs

- The initial signs of phosphorus poisoning are referable to gastrointestinal irritation and the onset may be almost immediate or may be delayed up to several hours. There is severe abdominal pain, profuse vomiting and possibly hematemesis.
- Thereafter there is a period of apparent recovery of a few hours up to 4 days. Then the abdominal pain and vomiting recur, this time accompanied by jaundice. These signs may last several days and then be followed by delirium, convulsions in some animals, then coma and death. Alternatively the animal may make a recovery without any neurologic signs. Horses and poultry may exhibit a paralytic-like weakness without other definitive signs. The latter stages are attributable to profound liver and kidney failure which terminates in shock.
- Oliguria and anuria may occur.

Clinical Pathology

Clinical pathologic alterations antemortem may include hypoglycemia, hematuria, and proteinuria.

Lesions

Lesions include inflammation of the gastrointestinal tract, stomach, intestines and skin when dermal exposure has occurred. There is also fatty degeneration of the liver, muscles and endothelium of blood vessels with secondary extravasation of blood into the subcutaneous tissues, skin and muscle. There may also be hematoma formation. Jaundice is common.

Diagnosis

Diagnosis is based on history of exposure, clinical signs, odor and luminescense of the breath, vomitus, and stomach contents and lesions. Phosphorus content in the vomitus or intestinal tract may be determined. In animals surviving the first day, feces may be preferred over stomach contents (seal in a jar and freeze before transport to the laboratory maintaining a frozen state).

Treatment

- Treatment of dermal exposure is initiated by brushing all traces of dry phosphorus from the skin. The white or yellow phosphorus may then be removed from the skin by washing the skin with a copper sulfate solution. The skin is then repeatedly washed with large volumes of water. Oily substances are contraindicated due to the enhancement of absorption.
- For oral exposure, careful gastric lavage is preferred to emesis due to the corrosive action of phosphorus. Lavage with potassium permanganate has been recommended; however, there is no data to confirm the benefit of this treatment. Alternatively, lavage with 0.2% copper sulfate may be performed. As with dermal exposure oils are contraindicated due to facilitation of absorption; however, activated charcoal and saline cathartics are highly recommended.
- For hepatic and renal failure, cystine and a high carbohydrate diet which is low in protein are recommended. In addition, comparatively high doses of B-vitamins and ascorbic acid tend to lessen the severity of the liver failure. Fluids are indicated to increase the urinary output. Naturally, liver and kidney function tests are monitored early on for comparison to subsequent values.
- For hypotension, fluids are administered and if the animal is still unresponsive (with regard to perfusion), then dopamine is administered.
- Hypoprothrombinemia and hemorrhage is treated with vitamin K_1 and, where needed, with whole blood or plasma tranfusion(s).

Carbon Tetrachloride

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
All species	Hours to days	Days to permanent damage; often lethal but toxicoses are rare	

Source

- Carbon tetrachloride has been used in the treatment of internal parasites especially in the removal of adult liver flukes from sheep.
- It is also an industrial solvent and used to be available for removal of stains from clothing, etc.
- By itself, $CC1_4$ is not as toxic to insects in grains as carbon disulfide (CS_2) and other effective fumigants. However, until very recently when its use was banned, it was used alone and especially in combination (to reduce the fire hazard associated with fumigation) with either CS^2 or ethylene dichloride. When grains are inadequately ventilated after treatment, the likelihood of toxicosis exists. Lower temperature increases the time necessary for adequate ventilation.
- Related anthelminitics may cause similar effects as $CC1_4$ but are usually less toxic. Nevertheless, similar precautions should be observed with:
    - N-butyl chloride.
    - Tetrachloroethylene.
    - Tetrachloroethane.
    - Hexachloroethane.

Structure

$C\text{-}Cl_4$.

Susceptible Species

Carbon tetrachloride is especially toxic to swine. Cattle are somewhat more sensitive than sheep, but individual sheep may be quite sensitive. Poultry are most tolerant.

Toxicity

- LD_{50} rat (acute oral) is 2,800 mg/kg.
- LC_{50} in feed (mouse) is 9,528 ppm.
- Poisoning can occur from inhalation, oral or topical exposure.
- Inhalation: a few minutes of exposure to 3,000 ppm is tolerated while levels of 12,000 ppm for 15 minutes cause nonlethal toxicity (see Osweiler et al., 1985).
- Carcinogenic.

Factors Affecting Toxicity

- Selenium supplementation may lessen susceptibility.
- Diets high in protein increase the toxicity of carbon tetrachloride and diets low in protein decrease the toxicity.
- Consumption of plants which are hepatotoxic or which contain oxalates tends to increase the effect of $CC1_4$ on the liver.
- Experimental exposure to enzyme inducers, such as phenobarbital, DDT, chlordane or dieldrin increase the toxicity of $CC1_4$. In man, concurrent ethanol ingestion increases susceptibility to $CC1_4$.
- Age is another factor, in that lambs of less than 5 months are predisposed to carbon tetrachloride toxicosis. Ewes which are suckling lambs are also at increased risk. Fat ewes and underweight animals are less tolerant of $CC1_4$.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Carbon tetrachloride is slowly absorbed from the intestine in unchanged form. Dividing the dose and administering $CC1_4$ in repeated small amounts or administration in conjunction with fat or a high lipid diet increases absorption and increases toxicity.
- $CC1_4$ is eliminated via expired air, via the kidneys (primarily after metabolism), and especially via the bile as metabolites.
- Increases in environmental temperature increase panting which enhances removal and decreases toxicity. Simlarly, lower environmental temperatures increase toxicity.

Signs

- Large doses of carbon tetrachloride are followed by narcosis similar to that associated with chloroform.
- Additional signs include diarrhea, incoordination, and sometimes vascular collapse in 24 to 48 hours. Anorexia, dullness, blood stained feces, constipation then diarrhea, possible hypocalcemia and collapse may precede death.
- The most important toxic effect of $CC1_4$ is liver damage. Small doses cause fatty degeneration which, in sheep, may be seen when the animals die 4 days or more after exposure.
- Large amounts cause centrilobular necrosis, which may be observed in sheep dying in 3 days or less. Hepatotoxicity may be associated with swelling and tenderness in the liver antemortem. Lethality due to hepatic damage most often occurs during the 2 weeks following exposure.
- In fatal cases, renal damage may be more severe than liver damage. Casts, proteinuria, hematuria, oliguria and increases in BUN may be present.
- If enough tissue remains functional to allow survival, damaged hepatocytes may undergo resolution and normal function may sometimes be reestablished within about 8 days. Similarly, renal function may be restored within about 3 weeks; however, complete return of liver and kidney function may take up to a year.
- It is recommended that sheep be fed hay a few days before and after treatment with $CC1_4$ to kill liver flukes.

Lesions

- Gastroenteritis confined especially to the abomasum and upper small intestine.
- Hepatic congestion, fatty degeneration or centrilobular necrosis.
- Renal congestion as well as cloudy swelling and necrosis in renal tubular epithelium.

Note - In acute cases may see no liver or kidney lesions.

- With aspiration due to faulty drenching with carbon tetrachloride or due to capsule rupture, inhalation pneumonia is seen.
- Repeated small doses of $CC1_4$ may result in hepatic cirrhosis.

Treatment

- Very recent exposure-emetics when not contraindicated.
- Recent exposure-where emesis not indicated-gastric or rumen lavage.
- Activated charcoal and a saline cathartic.
- Artificial respiration if anesthetized.
- IV dextrose in large amounts reportedly delays the hepatotoxic effects.
- Calcium solutions are reportedly beneficial.
- Osmotic diuretics and fluids are used to increase urine output.
- High carbohydrate diet.

Note - Epinephrine and norepinephrine are contraindicated as they may induce ventricular fibrillation.
Note - Heptatic coma may be treated by efforts to lower the blood NH_3 concentration. Steps include:

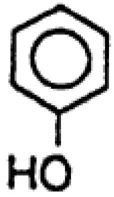
- Decreasing protein intake.
- Prevent ammonia absorption from the stool by daily administration of milk of magnesia or sodium sulfate.
- Oral neomycin to lessen intestinal bacteria capacity to break down proteins.
- Peritoneal dialysis.
- Avoid chlorothiazide.

Phenolics and Coal Tar

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
All species	Hours to days	Days to permanent damage; often lethal	

Sources

- Phenol itself is used as an agent to produce protein precipitation and has been recommended for the cauterization of corneal and oral ulcerations.
- Flooring materials containing over 6% phenol are toxic to pigs up to 4 kg BW.
- Lignite pitch and bitumen flooring is also toxic because of the high phenol content, while mineral-oil bitumen flooring is not a problem.
- Coal tar is encountered primarily as a result of the consumption of "clay pigeons" which are usually yellow and black, bowl-shaped targets used to practice with shotguns. Coal tar pitch may also be encountered as a result of its use as a coating on wood or even metal surfaces.
- Coal tar itself is a by-product of the destructive distillation of coal. Constituents include benzene, toluene, naphthalene, anthracene, xylene and other aromatic hydrocarbons including phenol, cresol and other phenolics, ammonia, pyridine and other organic bases and thiophene. It is an almost black, thick liquid or semisolid material. In clay pigeons it is mixed with ground limestone.
- Tar paper is another source of coal tar pitch which has proven capable of causing toxicosis.
- Sources of phenols also include creosote, which may also be called wood creosote or beechwood creosote. Creosote from coal tar also exists and the latter is more toxic than the wood derived types. Wood creosotes have been used as antiseptics, expectorants, parasiticides, deodorants, gastric sedatives and gastrointestinal antiseptics although these uses are all largely out-of-date and no longer employed. Creosote from coal tar has been widely used for impregnating wood to protect it from rot and worms, and it is also used as a fungicide, germicide, insecticide and disinfectant.
  - Wood creosote contains creosol (4-hydroxy-3-methoxy-l-methylbenzene) and a mixture of other phenols.
  - Coal tar creosote contains m-cresol (3-methylphenol) and p-cresol (4-methylphenol) and other liquid and solid aromatic hydrocarbons and tar acids and tar bases.
  - Creosote is a restricted-use pesticide (Federal Register, February 1986).
- Other products include more purified cresols (hydroxytoluenes, cresylic acid, tricresols), naphthol, menthol, thymol, guiacol and resorcinol which is synonymous with 1,3 benzenediol. Some Lysol products contain o-phenylphenol.



Phenol

Toxicity

- Oral LD_{50} of phenol itself is approximately 0.5 g/kg except in the cat which is more sensitive.
- The degree of the toxicity of the phenolics varies widely with phenol itself being one of the most toxic. The cresols have approximately the same toxicity as phenol, but the ortho and para isomers are even more toxic. These compounds are apparently slightly more corrosive than phenol, but are absorbed more slowly and may have a bit milder systemic effect.
- LD_{50} of clay pigeons in swine: approximately 1 g/kg for several days.

Mechanism of Action

Phenols are protoplasmic poisons causing coagulation necrosis of many tissues. Capillary damage, hepatorenal necrosis and neurotoxicity may occur. Phenol also causes considerable stimulation of the respiratory center which may result in respiratory alkalosis. As the syndrome progresses however, a metabolic acidosis may develop. The clinical course and severity of toxicosis is highly dependent upon the type of phenolic and the degree of exposure as well as the species and age of animal exposed.

Absorption, Distribution, Metabolism and Excretion (ADME)

Phenols are absorbed after oral or dermal exposure and are excreted at least in significant measure as glucuronide conjugates.

Signs

- The clinical course depends upon the amount and type of phenolic.
- Contact with concentrated phenol causes obvious white discoloration of the contacted skin or mucous membranes, however, many of the derivatives do not have this effect.
- Phenol causes considerable stimulation of the respiratory center which may result in a respiratory alkalosis. In humans poisoned with phenol, respiratory alkalosis or metabolic acidosis (possibly later in the syndrome) may be seen.
- Early in phenol poisoning, there is incoordination and mild muscle fasciculations in some animals. The condition often progresses to coma and then respiratory failure.
- Seizures, coma and death are more common in cats.
- Icterus may be present as a result of hepatic damage or sometimes hemolysis.
- Some animals experience renal failure.
- Rapid death may be the primary presenting complaint in swine after exposure to a source of coal tar.
- Some coal tar poisoned swine, however, live for several hours or days after the onset of signs including weakness, recumbency (sternal) and depression. The respiratory rate is increased and there is a tender abdomen which can be detected by digital pressure. A secondary anemia and visible icterus may be seen.
- Methemoglobinemia sometimes occurs in phenol poisoned animals.

Lesions

- In coal tar poisoning of swine, the liver is usually very enlarged with a varigated mottling and engorgement. It is often quite friable and the lobular pattern is exaggerated. Some lobules are dark red; other lobules are yellowish. The mottling is especially apparent on the cut surface. The lymph nodes of the abdominal cavity become enlarged and hemorrhagic. Often the kidneys are enlarged and pale. Generalized icterus is common.
- The corrosive effects of phenols or cresols may be seen in the oral and upper gastrointestinal tracts of orally exposed animals. These tissues may initially be whitish, having a cooked egg appearance or may be edematous and hemorrhagic. At death there is often severe centrilobular hyperemia, fatty degeneration and necrosis of the liver. Renal damage is also common. Renal tubular degeneration and necrosis may be seen microscopically.

Diagnosis

- The clinical signs, lesions and the history of exposure may suggest the etiology. There may be an aromatic lamp oil odor to the breath.
- A positive rapid presumptive test may be performed to confirm the diagnosis: 10 ml of urine is mixed with 1 ml of 20% ferric chloride. A purple color indicates the presence of phenol.
- Serum, urine or kidney may be analyzed for the presence of phenol at selected toxicology laboratories.

Treatment

- Only after assessing the severity of mucosal damage may emetics and/or gastric lavage be considered. If severe damage is present, these techniques should not be used.
- Activated charcoal and a saline cathartic may be worthwhile and are recommended.

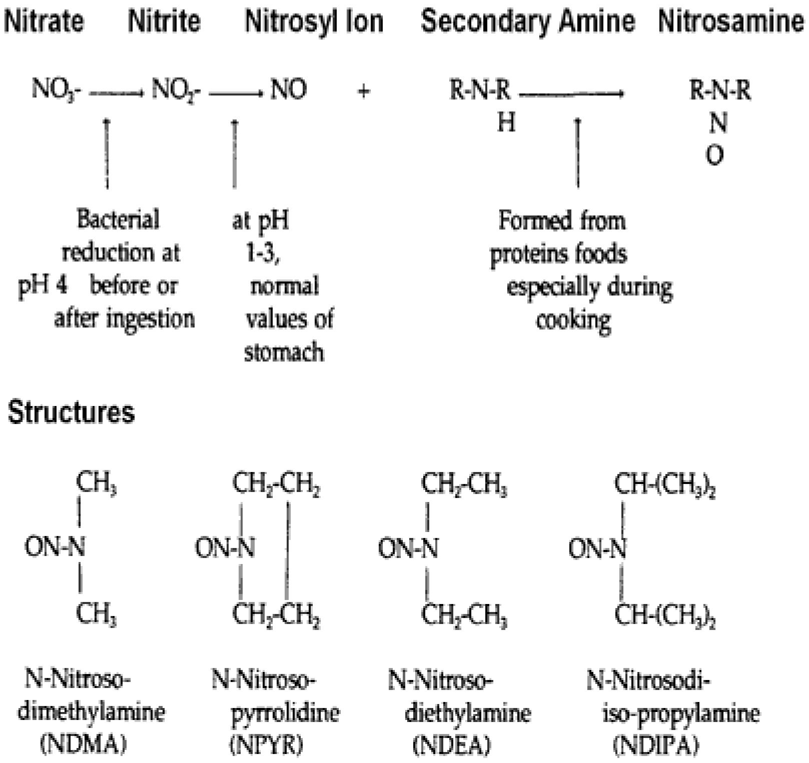
- In the past, poorly absorbed oils such as olive oil were recommended, although mineral oil was avoided since it would not dissolve phenol.
- For dermal exposure, the preferred agent for dilution and removal is polyethylene glycol or, as an alternative, glycerol (= glycerine) prior to washing. Whether or not one of these agents can be used first, the animal is bathed with generous amounts of a liquid dish detergent (**not** the automatic dishwasher type) and thoroughly rinsed with water. This may be followed by castor oil used as an additional cleansing agent and then additional bathing and finally by 0.5% sodium bicarbonate soaked dressings. It is wise to avoid oily dermatologic preparations other than castor oil, early in the course of phenol toxicosis in small animals as these may enhance the absorption of phenol.
- Additional therapy may involve respiratory support and control of shock and metabolic acidoses although such severely affected animals may warrant a poor prognoses in many cases.
- Fluid therapy is indicated since phenolic metabolites are eliminated in the urine.
- For oral exposure, demulcents such as milk and egg are indicated after the use of activated charcoal to help protect injured mucous membranes from further damage.
- Acetylcysteine has been recommended for animals with methemoglobinemia at a loading dose of 140 mg/kg, followed by 70 mg/kg QID per os for 3 days.
- Steps should be taken to prevent further exposure. Clay pigeons in fields for up to 35 years have resulted in serious outbreaks of toxicosis in swine.

Nitrosamines

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
Sheep, human	Hours to chronic	Weeks to permanent damage, potentially lethal; toxicoses are rare	

Sources

- The nitrosamines have been known for a long time, but the extreme toxicity of members of this group of chemicals has only recently been recognized. Generally, they serve no useful purpose.
- Nitrosamines are readily formed when nitrite-preserved meats are cooked at exceedingly high temperatures.
- The nitrosamines also can be readily synthesized in the laboratory and apparently under biological conditions. The 2 basic chemicals required for the production of nitrosamines, secondary amine and nitrite, can form nitrosamines spontaneously in the warm acid conditions of mammalian stomachs.
- Few reports of nitrosamine poisoning have been documented in domestic animals. In one instance, a large number of sheep were poisoned following consumption of nitrate treated fish meal in which nitrosamines had formed.
- A similar outbreak of nitrosamine toxicosis occurred in mink fed fish meal.
- In humans, there is also concern, since nitrosamines may form from nitrates and secondary amines in the stomach. This may occur after ingestion of antacid drinks which keep the stomach pH temporarily above 4, or after ingestion of nitrite and overheated protein foods.
- The proceses of formation of nitrosamines *in vivo* are shown below.


Nitrate
Nitrite
Nitrosyl Ion
Secondary Amine
Nitrosamine
NO3-
NO2-
NO
+
R-N-R H
R-N-R N O
Bacterial reduction at pH 4 before or after ingestion
at pH 1-3, normal values of stomach
Formed from proteins foods especially during cooking
Structures
N-Nitroso-dimethylamine (NDMA)
N-Nitroso-pyrrolidine (NPYR)
N-Nitroso-diethylamine (NDEA)
N-Nitrosodi-iso-propylamine (NDIPA)

Signs

The signs of nitrosamine toxicosis are compatible with acute, subacute or chronic hepatotoxicity.

Lesions

- Nitrosamines are, for the most part, strongly hepatotoxic and many synthetic nitrosamines are known to be carcinogenic, especially affecting the liver.
- In the sheep mentioned above, severe liver damage occurred.

Prevention

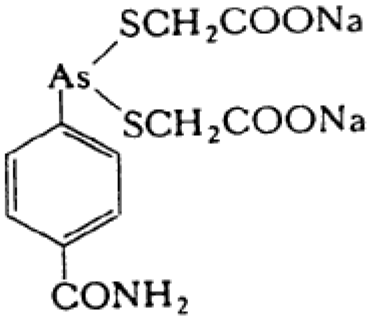
In meats preserved with nitrites, sodium erythrobate and/or ascorbic acid are added to limit formation of nitrosamines.

Thiacetarsemide Sodium (Caparsolate ®)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
Dogs	One day to 3 weeks	Several days to weeks; often lethal	

Source

Thiacetarsamide is an arsenical used to kill adult heartworms in dogs.



Signs

- Adverse reactions to thiacetarsemide apart from pulmonary thromboemboli occurring from 5 to 30 days posttreatment are comprised primarily of hepatotoxicosis and, to a lesser extent, of nephrotoxicosis.
- Clinical signs include extremely persistent vomiting, icterus and orange urine. Affected animals may become persistently anorectic and hepatic encephalopathy is possible.
- The earliest sign of hepatotoxicity is bilirubinuria. It has been suggested that bilirubinuria (regardless of severity) is not an indication to stop a treatment regimen if only one dose remains and if there are no other signs of illness. However, bilirubinuria which occurs after only the first or second dose indicates the need to terminate treatment.
- Icterus, on the other hand, is always a sign signalling the need to terminate the use of thiacetarsemide. Generally, animals for whom treatment is terminated may receive a full regimen of thiacetarsemide after a 4-week rest and these individuals usually tolerate the regimen very well.

Clinical Pathology

- About 20% of all dogs with normal serum glutamine pyruvic transaminase (SGPT) and serum alkaline phosphatase (SAP) values prior to thiacetarsamide treatment develop elevations above the normal range after treatment. Generally the elevation occurs on the first day or 2 after treatment but the SGPT values decline within 7 days.
- Preexistant elevations of SGPT, SAP or BSP are not indications to delay adulticidal treatment, and microfilaricide treatment before adulticide treatment is not indicated.
- Thiacetarsamide induced renal failure is more likely in dogs with previously compromised renal function. Therefore, the BUN and urinalysis results should be evaluated before treatment.

Treatment

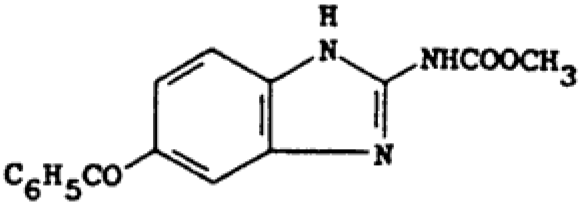
- Supportive care includes rest and a high carbohydrate diet such as K/D. Tigan rectal suppositories, dosage adjusted according to weight, are useful in controlling vomiting. B-vitamins and liver sparing agents, although not of proven benefit, may be given.
- Although the benefit of British Anti-Lewisite BAL (Dimercaprol) or other arsenic chelators would seem likely, its use is not widely documented (if at all) in the management of thiacetarsemide.

Mebendazole - (Telmin ®, Telmintic ®, Vermox ®)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
Dogs	Around 2 weeks	Days to weeks; often lethal	

Toxicity

Generally, the anthelmintic mebendazole is of low toxicity and has a wide margin of safety in animals. Nevertheless, there have been reports of mebendazole toxicosis in a group of Doberman Pinschers and Dachshunds and in a Labrador which were dosed at the recommended therapeutic level for 5 days.



Mebendazole

Signs

- Develop at approximately 2 weeks after treatment.
- Anorexia, depression, vomiting, icterus, hemorrhagic diarrhea and sometimes dehydration.

Clinical Pathology

Elevations occur in SGPT, alkaline phosphatase, and bilirubin (especially direct bilirubin). Appart from the effects of dehydration, blood counts were unaffected.

Lesions

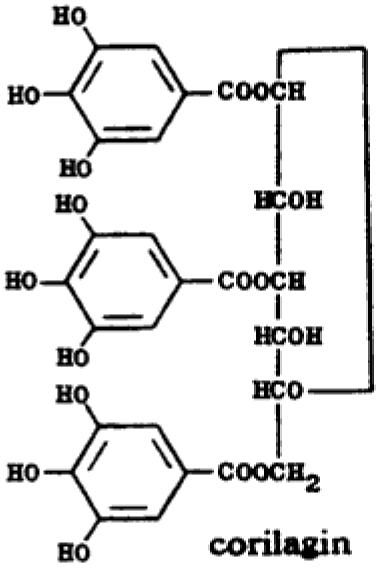
- Severe, generalized, centrilobular hepatic necrosis with loss of hepatocytes, sinusoidal collapse and replacement by hemorrhage.
- Hepatocytes near portal triads and bile duct epithelia were vacuolated and had swollen nuclei.
- Occasional inflammatory cell infiltrates were present.
- Overall the hepatic lesion was classified as a cytotoxic form of massive, hemorrhagic, necrotic hepatitis.
- In contrast to these clinical effects, experimental attempts to reproduce these findings were unrewarding. The effect of repeated and exaggerated mebendazole administration was evaluated in dogs with and without experimentally induced altered liver function. Irish Setters and Toy Poodles were dosed at 1, 3, and 5 times the therapeutic dose (22 mg/kg) of mebendazole for 17 days, without any effect on the liver. Mixed breed dogs that received increasing doses of mebendazole at 11 to 110 times the therapeutic dose for 2 months did not show adverse effects and remained in good health throughout the experiment. There was no substantial evidence that carbon tetrachloride-induced liver changes were exacerbated by subsequent repeated treatments with mebendazole at 15 times the therapeutic dose.
- Additionally, in dogs in which liver function was compromised experimentally by glutathione depletion or microsomal enzyme induction, administration of mebendazole at this same dosage for 30 days did not result in any hepatotoxic effect. When mebendazole was given at 15 times the therapeutic dose prior to a hypoxic episode in dogs pretreated with a barbiturate and high protein diet, there was no evidence of any adverse effect on liver function.
- These metabolic manipulations, in conjunction with mebendazole administration, failed to reveal any mechanism of hepatic dysfunction associated with mebendazole treatment. Unrecognized factors appear to be involved with the rare cases of hepatic dysfunction that have been reported after mebendazole administration. Only careful documentation of field cases and further laboratory research can identify these factors.
- For these reasons mebendazole toxicosis of dogs is considered an idiosyneratic drug reaction.

Tannic Acid

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatotoxic Chemicals and Drugs
All species	Hours to days	Days to weeks; potentially lethal	

Sources

- Tannic acid has been recommended for forming insoluble salts with some heavy metals, for alkaloid and glycoside inactivation, for the treatment of burns and diarrhea, and has been combined with barium for use in barium enemas. These uses are losing favor with many toxicologists.
- It may also be encountered in children's chemistry sets and is used for "tanning" hides in leather processing.
- Tannic acid is also used as an astringent. Astringents are agents which precipitate proteins, but have little penetrating ability, so that their primary effects result from altered cell surface characteristics. Consequently, the cell itself remains viable, but its permeability is greatly reduced.



Tannic acid

Absorption, Distribution, Metabolism and Excretion (ADME)

- Tannic acid N.F. is formed from a number of glycosides (or tannins) comprised of glucose and tannic acid. The rate of hydrolysis of the glycosides and release of tannic acid varies with different plant sources. The most common tannic acid, which is a powder, soluble in water, glycerine, or alcohol, is derived from nutgalls of oak trees. A tannic acid glycerite, which is 20% tannic acid and 1% sodium citrate in glycerine is also available. Protected or slow release tannic acid formulations are more hazardous, since more of the tannic acid tends to be absorbed.
- In the gastrointestinal tract, tannic acid is converted to gallic acid, which is nonastringent, and glucose, and is then absorbed. Gallic acid is then degraded in the body and a small amount is excreted in the urine. Toxicosis results when sufficient intact tannic acid is absorbed.
- Although widely effective in precipitating some metals, and inactivation of some alkaloids, there are several members of these classes of toxicants which are not precipitated as tannates. These include cocaine, nicotine, physostigmine, atropine, morphine, arsenic, antimony and mercury. In addition, tannic acid interferes with the adsorbent action of activated charcoal.

Signs

- Ingestion of large doses of tannic acid can produce severe gastroenteritis and abdominal pain.
- Although widely used in barium enemas, 5 deaths in children and 3 deaths in adults, apparently as a result of tannic acid-induced hepatic necrosis have been reported.
- Toxicosis has also resulted from absorption of intact tannic acid from the intestine after large doses are consumed and after cutaneous absorption of tannic acid from treated burned areas.

Treatment

- Treatment of tannic acid ingestion is comprised of administration of milk to dilute the tannic acid followed by an emetic, unless contraindicated. When emetics are contraindicated or ineffective, lavage should be employed.
- Gelatin or egg white may be instilled in the initial fluid to form insoluble tannates, which are then removed by the lavage.
- Emesis or lavage is followed by activated charcoal and a saline cathartic.
- Supportive therapy for liver failure is indicated since hepatic necrosis is the usual lethal mechanism in tannic acid toxicosis regardless of the route of administration.
    - At the present time there are few indications for tannic acid for which safer and more effective treatments are not available.

Note - Gallotannins (and possibly other constituents) which are encountered by livestock consuming oak buds or acorns are associated with effects largely on the gastrointestinal tract and the kidneys.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
Copper (also: See Toxicants that Cause Hemolysis)	Sheep, cattle, certain breeds of dogs	Hours to Chronic	Days to permanent damage, often lethal	Full Table for Hepatotoxic Chemicals and Drugs
Dialkyltins (including metabolites of trialkyltins)	Wildlife	Chronic	Chronic	
Acetaminophen	Dogs, cats	1 - 3 days	Days to permanent damage; often lethal	
Formaldehyde	Dogs	Hours to days	Days to permanent damage; often lethal	
Carbon disulfide (also: See Toxicants with Mixed Effects on the CNS)	All species	Hours to days	Days to permanent damage; often lethal	
Halogenated hydrocarbons including halogenated dibenzodioxins (See Toxicants that Affect the Skin, Other Organic Compounds)	All species, especially top aquatic predators	Chronic	Weeks to permanent, potentially lethal	
Pennyroyal oil (Used as insecticide)	See Organic Compounds that Affect the Lungs			

Mycotoxins that Affect the Liver

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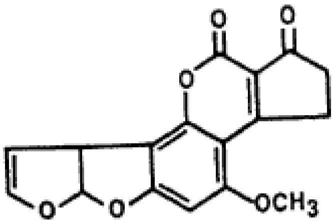
Aflatoxins

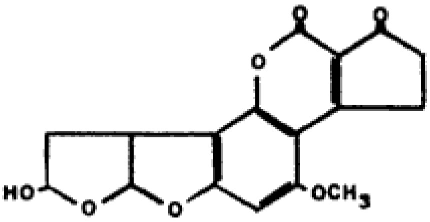
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Mycotoxins that Affect the Liver
Most Species	Days to Chronic	Weeks to permanent damage, potentially lethal	

Sources

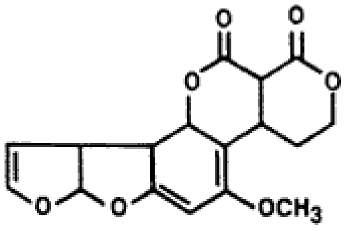
- Aflatoxins are secondary mold metabolites produced by some strains of *Aspergillus flavus* and *A. parasiticus*.
- Chemically they are polycyclic furan compounds possessing intense blue or green fluorescence under long wave UV light.
- Although at least 13 aflatoxins have been identified, 4 (B_1, B_2, G and G_2) are most common.
- Aflatoxin tends to be produced in highly nutritious foodstuffs at high moisture concentrations and warm environmental temperatures. Aflatoxin can be produced in conditions of 85% relative humidity (e.g., corn moisture content of 15 to 28%) and temperatures over 55º that persist for over 48 hours. Most problems result with sustained high temperatures of 78 ºF or more.
- Under these conditions, peanuts, corn, walnuts, pecans, almonds, cottonseed and grain sorghum are more susceptible to *A. flavus* contamination than soybeans, wheat, rye and oats.
- *A. flavus* may grow on corn in the field as well as in storage. Corn is dried in order to create an internal environment of less than 85% relative humidity. This degree of relative humidity is the minimum for significant aflatoxin production. Of course relative humidity is dependent upon evaporation which is a variable greatly affected by increases in temperature. For these reasons, it is sometimes possible to store corn in the mid to late fall and early winter at somewhat higher moisture concentrations than could be tolerated in September. At usual seasonal temperatures the 85% relative humidity figure will not be exceeded if corn moisture concentrations in September, October and November do not exceed 17, 18 and 19%. However, just blowing air over corn at these or higher moisture concentrations will be inadequate if higher than normal temperatures prevail.
- Most problems in the Midwest occur as a result of a drought and insect damage, which allow the mold to get started, followed by prolonged hot weather. Thereafter improper drying and warmth after harvest are major contributing factors resulting in toxin production in corn.
- Findings in biased samples sent for aflatoxin analysis in 1983 (a drought year).
  - 1982 (a normal year) **Suspect** corn - less than 1% of that Illinois corn tested contained detectable concentrations of aflatoxin.
  - 1983 **Suspect** corn - approximately 70% were black light positive - and of these most had at least a little aflatoxin.
  - Of 90 samples of 1983 **Suspect** corn tested by Centralia:
    - Eight percent contained over 250 ppb aflatoxin.
    - Forty percent contained 50 to 250 ppb.
    - Sixty percent contained less than 50 ppb.
    - One sample contained 12,000 ppb (12 ppm).
  - If an unbiased sample was collected a lesser percentage would have been found.
  - In 1988 (another drought year), aflatoxin at up to 3,500 ppb was reported.
  - In 1995, Texas corn samples were found to contain aflatoxin at up to 5,000 ppb.
- Sometimes "high moisture" corn may not be high enough in moisture to ensile. Consequently, fungal growth and toxin production may occur instead.



Aflatoxin B_1



Aflatoxin B_2



Aflatoxin G_1

Factors Affecting Sensitivity

- The sensitivity of animals varies according to age and species as shown.
- Young animals are generally more sensitive than adults.
- Sensitivity to aflatoxin.
  - Most sensitive ----------------------------------- Least sensitive.
- Among domestic animals: ducklings, trout, dogs, pigs, cattle, sheep, chickens.
- Among livestock: piglets, pregnant sows, feeder pigs-calves-horses, finishing hogs, lambs, dairy cows (residues in milk possible), feeder cattle, mature sheep.

FDA Limits Set for 1988 Corn Crops (Pertains to Corn Rather than Feed)

- In corn, a maximum of 20 ppb aflatoxin is allowed in interstate shipments unless special FDA permission has been obtained for a higher aflatoxin level. This is ordinarily done when drought conditions cause widespread contamination.
- Set for 1988 corn crop.
  - 20 ppb maximum allowable for corn destined for human consumption, for interstate transport, or to be fed to dairy cattle or immature animals.
  - 100 ppb - Approved for corn destined for consumption by breeding cattle, breeding swine, and mature poultry.
  - 200 ppb - Approved for corn destined for finishing swine (greater than 100 lb).
  - 300 ppb - Approved for corn destined for finishing cattle (feedlot).
  - Individual states can act at levels below the above levels if they deam it necessary.
  - Blending - Contaminated corn can be blended with clean corn for animal feed use **only** and must be approved by the FDA regional office.
  - FDA limit in milk.
    - 0.5 ppb of aflatoxin M_1 = the actionable level in milk.
    - Milk is routinely monitored for aflatoxin M_1 by spot checking followed by trace back to the source farm(s).

Toxicity

- Swine.
  - LD_{50} aflatoxin B_1 = 0.8 mg/kg BW.
  - At 400 to 600 ppb in feed, severe clinical disease in feeder pigs.
  - Adults - 450 ppb in feed of sows and boars, had no effect on spermatogenesis, litter size, piglet quality or lactation.
  - Chronic toxicity, feeders 300 to 400 ppb in feed.
  - Less than 223 ppb, no effect.

ADME and Residue Considerations (See FDA Limits Above)

- Aflatoxin M_1 is the principal aflatoxin residue in meat and milk. It retains only a limited amount of the toxic potential of the parent compound.
- In exposed animals, residues in meat products may sometimes be of concern. Rations with less than 100 ppb aflatoxin will yield muscle tissues containing less than 0.5 ppb aflatoxin, the actionable concentration in human foods although kidney may be considerably higher M_1, the actionable concentration in human foods although kidney may be considerably higher. Generally even at

somewhat higher concentrations, 5 days on clean feed will allow depletion of residues from muscle to acceptable concentrations.

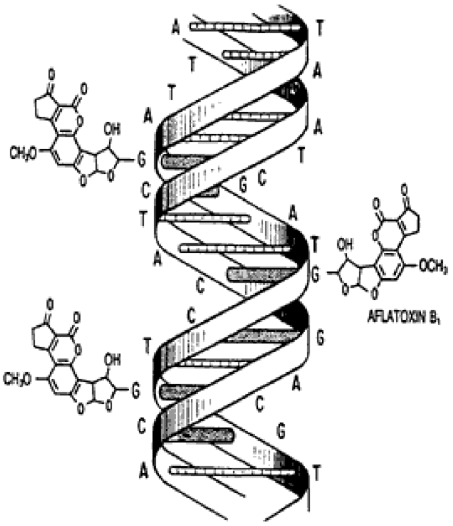
- Metabolite (epoxide) produced in the animal is the actual carcinogen.

Mechanisms of Action

- Aflatoxins are potent hepatotoxins and hepatocarcinogens.
- May react with and modify the DNA template to interfere with RNA transcription or may specifically inhibit RNA polymerase which would also impair transcription.
- Also increase the rate of RNA breakdown by alteration of lysosomal membranes resulting in the release of ribonuclease from lysosomes.
- May stimulate the alkylation of RNA by stimulation of RNA methylase.
- As a result of a reduction in the active forms of RNA, protein synthesis is secondarily impaired.
- Effects include hemorrhage, immunosuppression, stunting and liver damage.

Signs

- The early clinical signs of aflatoxicosis may be indistinguishable from signs of deoxynivalenol, T-2 toxin and a host of other disease syndromes. Thereafter the signs, clinical pathologic changes and lesions of aflatoxicosis often help in suggesting a diagnosis.
- Decreased feed efficiency is generally the first sign recognized at low concentrations.
- Reduced feed intake.
- Decreased growth rate.
- General unthriftiness.
- Rough, dull haircoat.
- May manifest as increase in prevalence, severity of or failure of therapy or vaccinations for infectious diseases such as:
    - Bloody dysentery.
    - Erysipelas.
    - Salmonellosis.
    - Pneumonias.
    - Failure to test feed, and antibiotic therapy after a (partial) diagnosis of an infectious disease, may result in a "partial" resolution of the clinical problem.
- Ascites.
- Hemorrhage and icterus.



Aflatoxin B_1 binds to DNA at the guanine base in liver cells, corrupting the genetic code that regulates cell growth. Out-of-control cells grow into tumors that eventually become cancerous. Drawing by G. Hedberg, USDA, ARS, National Animal Disease Center, Ames, Iowa.

Aflatoxin - Effects in Swine According to FDA*	
Parts per Billion	**Clinical Signs**
500	Reduced growth, liver impairment, appetite loss
1,000	Marked growth reduction; liver and kidney damage; petechial hemorrhages in muscles, viscera
2,000	Severe hemorrhage, bloody diarrhea, death in 1 to 3 days
Other Studies	
280	Decreased rate of gain and feed efficiency

***Note** - Animal ages not stated.

Clinical Pathology

- Feeder pigs become anemic (appear pale) or may appear icteric.
- Abnormally elevated SGOT, SGPT, alkaline phosphatase, ornithine carbamyl transferase, isocitric dehydrogenase.
- Decreased albumin and A/G ratio.
- Increased prothrombin time (acute syndromes).

Lesions

- Acute form in swine.
  - Icterus.
  - Ascites ± fibrin.
  - Intestinal hemorrhage.
  - Subcutaneous and muscular hemorrhage.
- Subacute or chronic (300 to 400 ppb of aflatoxin in young swine feed).
  - Generally debilitation.
  - Pallor or icterus.
- Decreased thymus size in very young.
- Variable ascites.
- Gross hepatic lesions-subacute.
  - Pale yellow to orange.
  - Friable or firm.
  - Granular or sometimes nodular.
  - Gallbladder edema in some swine.
- Gross hepatic lesions-chronic.
  - Fibrosis.
  - Regenerative nodules.
- Histopathologic hepatic lesions.
  - Biliary hyperplasia.
  - Hepatocellular swelling.
  - Hepatic lipidosis proceeding to vacuolation.
- Thymic involution.

Diagnosis

- When conditions are favorable for the production of aflatoxin grain elevators often utilize black light screening of corn in order to assess the possibility of aflatoxin occurrence in the grain. Several considerations must be understood when interpreting black light tests of corn. As shown in this table, all positives should be followed up by a more specific test to identify and quantitate any aflatoxin actually present.
- Black light test: factors.
  - Significant number of false positives but few false negatives.

    - Indicates the present of a derivative of kojic acid, a product that signals the growth of *Aspergillus*, not aflatoxin.
    - Remains positive only **temporarily**. Drying and storage can degrade the compound so that negative tests are likely when sampled thereafter.
    - Samples with only one glowing kernel have had up to 4,000 ppb aflatoxin.
    - Others - glowing kernels all through have had 30, 40, or 50 ppb.
    - Crack corn (do not grind) before doing black light test.
    - Follow up positives with laboratory analysis for aflatoxins.
- In Illinois, at least, a lot of elevators do black light screening in drought years and sometimes reject black light positive corn. Whether this succeeds in preventing storage of aflatoxin containing corn depends upon the diligence of the elevator personnel. However, some if not many elevators will not reject anyone as to do so means a loss of customers in future years. Sometimes, if purchased and black light positive, the elevator operators are aware of the risk and rapidly dry the grain to avoid further toxin production. However, this remains speculative.
- Methods of sampling feed for mycotoxin analysis.
    - 10-lb sample.
    - Sample all of bin, probe to get a representative sample.
    - Hot-spots, halfway down - or where ever you get greatest amount of fines may also be sampled.
    - Ship (for analysis) only.
        - At moisture concentrations of less than 14% -or-
        - Frozen -or-
        - Hand deliver.
    - Bank-frozen-labelled samples **before all fed**.
    - Samples sent for analysis should include a complete history in addition to labelling, detailing the sampling method.
- ELISA test (Quik-card ®, E-Z-Screen ®, Signal ®, Agri-Screen Aflatoxin ®) gives a + or - with the "cut-off" being at 20 ppb. These are now widely used at elevators and appear to be relatively accurate (all assays dependent upon how representative the samples are).

Treatment and Control

- Change to aflatoxin-free ration.
- Increase dietary protein.
- Vitamin B_{12} and Vitamin K.
- Selenium supplementation.

Recommendations

- Interpreting the significance of aflatoxin residues in feeds can be done on the basis of past field experiences, which are of course variable, and/or on the basis of experimentation. Therefore, recommendations as to the risk of given concentrations of aflatoxin feeds are dependent upon the interpretation of the toxicologist. The following are recommendations of the NAPCC.
- Feeds containing concentrations less than 50 ppb of aflatoxins can **generally** be fed safely to all animals.
- Feeds containing over 50 ppb aflatoxins should not be fed to weanling pigs.
- Concentrations greater than 100 ppb should not be fed to feeder pigs or breeding stock.
- Concentrations up to 300 ppb can generally be fed to finishing swine provided the animals are getting slightly increased protein supplementation, are having no other disease problems, and are brought onto the feed gradually.
- The feed should be free of detectable aflatoxins for several days before marketing animals.
- Due to sample variation, it is probably best to avoid giving aflatoxin contaminated feed to dairy cattle altogether. Although one can usually avoid exceeding the 0.5 ppb of aflatoxin M_1 level set by FDA by feeding less than 50 ppb of aflatoxins in the finished ration (dry weight basis). If the feed must be used, however, I would favor a maximum of 20 ppb aflatoxins in grain dry matter fed to dairy cattle.
- Do not feed over 50 ppb to calves less than 4 months old or over 100 ppb to calves 4 to 6 months old. Older calves and adult, nonbreeding cattle may be fed up to 300 ppb provided they are on a good plane of nutrition.
- Horses and dogs are comparatively sensitive, and it would usually be unwise to divert aflatoxin contaminated feed to their rations.
- Mature sheep are relatively resistant to aflatoxins.

- NovaSil ® (hydrated calcium aluminum silicates - HSCAS) has been approved by FDA **only** as an anticaking agent at up to 2% of a ration. Although **not currently approved** for a binding agent, this product has this added benefit. Research has shown that NovaSil ® binds aflatoxin and decreases its absorption. At concentrations up to 3,000 ppb Aflatoxin B, in the presence of NovaSil ®, at 0.5% of the ration, swine grew at rates similar to the controls, and the animals had no aflatoxin-associated lesions; however, aflatoxin-positive controls given 3,000 ppb B_1 all died. Poultry seem to benefit in a similar fashion; however, the efficacy of NovaSil ® in preventing residues of aflatoxin M_1 in the milk of dairy cows is considerably less than desirable.

Use of Contaminated Feedstuffs

- Feed affected foodstuff to less susceptible species and/or ages.
- Dilute with clean feed.
- Screen out broken kernels.
- Ammoniation of corn to reduce aflatoxin.
  - Ammoniation of corn is not done routinely in Illinois, however, for persons possessing large amounts of corn which is highly contaminated by aflatoxin, this alternative may be reasonable, provided several key considerations are made as illustrated.
- Ammoniation is a last resort only:
  - Corn turns brown.
  - Can be used only for animal feed.
  - Treated corn cannot be shipped across state lines.
  - Ammonia may corrode steel, galvanized metal, copper and brass.
- Hazards include:
  - Inhalation of mold spores and aflatoxin.
  - Ammonia lung-eye-skin irritation.
  - Ammonia vapor combustible.
  - Treated corn may cake up in equipment and not flow. Persons should not enter ammonia treatment bins "to help".
- Ammoniation:
  - May require rewetting of corn.
  - Slower process (longer ammonia contact necessary) in cool weather.

Avoidance of Mycotoxins (and Bacterial Spoilage)

- It is always best to avoid mycotoxicoses. Even corn initially toxin-free can become contaminated after it is delivered to the farm. Therefore, drying to below 14% moisture is essential. Screening can be used to remove broken kernels which are much more often moldy and will also reduce the amount of "fine material". "Fines" reportedly encourage mold and insect damage and inhibit aeration which delays drying.
- Low temperature drying of corn (by blowing air) that is field infected with molds is risky. Warm air temperatures can encourage mold growth. This method should, therefore, only be used when the temperature of the corn in the bin can be kept sufficiently cold to keep the humidity in the corn kernel below 85 °.
- Corn can often be stored at 15% H_2O, and it has approximately 180 days before it goes bad, so if sold at 150 days, it has the potential to go bad in 30 days or so. The resultant bacterial spoilage can greatly reduce palatability.
- Avoiding mycotoxins/minimizing problems.
  - Dry corn to less than 14% moisture.
  - Aerate regularly during storage to prevent condensation.
  - Harvest no more than 1 week after maturity.
  - Adjust harvesting equipment to minimize cracking of kernels.
  - Clean and decontaminate storage bins with Clorox ®/water 1:9.
  - Repair storage bins to avoid leakage; moisture can cause hot spots.
  - Clean the feeding system-feeders, augers, mixers, etc.
  - Do determine the history of corn your clients are getting.
  - They can avoid rewetting of corn or blending to increase moisture by the following procedures.
    - Buy corn quantity wise on a dry matter basis to remove the incentive to rewet and blend.
    - Keep corn in good condition-if necessary, redry it.

    - **Note** - Excessively dry corn may become brittle so that an increased amount of "fines" may occur enhancing the likelihood of fungal problems, and fungi may also enter damaged kernels; so this, too, must be avoided.
- Be sure that they:
    - Do submit appropriate samples for mycotoxin analyses when toxins are suspected.
    - Do have necropsies performed to establish that lesions compatible with **specific** mycotoxin poisonings are present.

Note - Reexamination of notes provided during the poultry course would be of value.

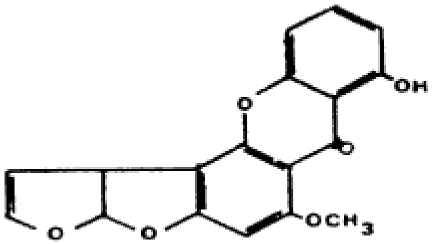
Hepatotoxic Mycotoxins: Sterigmatocystin, Rubratoxin, Sporodesmin, Penicillinic Acid
(Apart from Aflatoxins)

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
Sterigmatocystin	Most species	Weeks to chronic	Weeks to months; toxicoses very rare	Full Table for Mycotoxins that Affect the Liver
Rubratoxins A and B	Chickens; possible cattle and swine	Days to chronic	Unknown; toxicoses rare	
Sporodesmin	Cattle, esp. sheep	Chronic	Chronic reported primarily in Australia and New Zealand	
Penicillic acid	Swine	Chronic	Chronic; toxicoses rare	

1. Sterigmatocystin

Sources

- *Aspergillus versicolor*
- *A. rugulosus*
- *A. nodulans*
- *Bipolaris* sp.
    - Has produced sterigmatocystin on corn meal in concentrations as high as 1.2 gm/kg.
- Its racemate is produced by *P. luteum*



Structure of Sterigmatocystin

- Toxins containing same nucleus include:
    - Aflatoxins.
    - 5-methoxysterigmatocystin.
    - 0-methylsterigmatocystin.
    - Demethylsterigmatocystin.
    - Aspertoxins
    - Versicolorins.
    - Autocystins.
    - Sterigmatin.
    - Related toxins also include Bipolarin, Averufarin and Curvularin.

Toxicity

An LD_{50} of sterigmatocystin administered IP was 60 to 65 mg/kg in albino rats.

Absorption, Distribution, Metabolism and Excretion (ADME)

- In vervet monkeys 50% was eliminated in urine as its glucuronic acid conjugate.
- Readily epoxidized to probable actual carcinogen.
- Sterigmatocystin is 1/100 or less as potent as aflatoxin.

Lesions

- Hepatocarcinogen, necrosis of kidney and liver cells.
- Experimental administration was associated with squamous cell carcinoma production (topical application to rats).

2. Rubratoxins

Sources

- Rubratoxins A and B are produced by *P. rubrum* and *P. purpurogenum*. Both are common soil fungi.
- Sources of exposure - Cereal grains-primarily corn. The natural distribution of rubratoxin is not well established.

Toxicity

- LD_{50} values of rubratoxin range from 0.27 to over 5 mg/kg when given parenterally but were 400 to 450 when given orally to rats. The LD_{50} in chicken feed was 83 ppm.
- Males and females (rats) are equally susceptible; but **neonate** rats are 49 times as susceptible as adults.
- At sufficient doses, chronic dosing causes same effects; but animals getting subclinical doses had no lesions suggesting effective detoxification.
- Chicks.
    - 500 ppm rubratoxins (80% B) in diet was required to affect growth rate.
    - Dose of over 1,000 ppm in diet caused atrophy of liver and bursa of *Fabricius*.
    - (These levels **not** known to occur in nature.)

Mechanisms of Action

- Mutagen.
- Embryocidal.
- Teratogenic in mice.
- So far noncarcinogenic (rats).
- May potentiate the action of aflatoxin.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Long plasma half-life (days); most excreted in urine as parent compound (rats). Slightly less excreted in feces.
- This is contradicted in other studies which suggested a great amount was metabolized and excreted as CO_2.

Signs

- Clinical syndrome is similar to acute aflatoxicosis with anorexia, dehydration, diarrhea and possibly hemorrhage.
- It has been implicated in abortions in swine.

Lesions

- Acute and chronic syndrome characterized by hepatotoxic insult, nephrosis and general bleeding tendency. Congestion, hemorrhage and damage to liver, kidney and spleen.
- Early midzonal hepatic necrosis.
- Later extending to massive necrosis and replacement with hemorrhage with chronic doses.

3. Sporodesmin (Cause of Facial Edema)

Source

- *Pithomyces chartarum*, formerly called *Sporodesmium bakeri* which has an almost worldwide distribution and normally grows on any dead material.
- Sporodesmin derivatives have also been isolated.
- Toxicosis usually seen in late fall and early summer.
- Source of exposure - Ryegrass pasture Australia and New Zealand (on north part of island).
- Requires 100% humidity and 55 ºF for spore germination and rapid perfuse growth.
- Not known to be a big problem in USA.

Susceptible Species

- Bovine.
- Ovine. Sheep with resistance to facial edema have been bred in New Zealand.

Toxicity

- Toxic oral dose 0.4 to 0.7 mg sporodesmin per kg produces disease identical to field syndrome.
- Toxicity of hay decreases rapidly with proper storage.

Mechanisms of Action

- Hepatocellular damage - excreting of unconjugated sporodesmin in bile results in:
    - Occlusion of biliary system (acute cholangitis).
    - Terminates in fibrous obliteration of the ducts involved.
    - With resulting phylloerythrin accumulation which is normally secreted in the bile.
    - Photosensitivity results.
    - Get mild disorganization of organelles and triglyceride accumulation.

Signs

- Affected areas occur in light colored or sunlight exposed areas of the skin (ears and face).
- Edema of the skin, especially about the head.
- Serous exudation.
- Blistering, scab formation.
- Icterus.
- Anorexia, cystitis (early sign).
- Affected animals seek shade, and the apparent intense irritation causes the animals to rub the photosensitized areas on trees and posts; sheep may traumatize their eyes.
- Over 10 to 14 days there are stages of serous exudation, skin necrosis, and if animal recovers, sloughing of the necrotic tissue.
- The skin of the mammary glands on dairy cattle may slough in large pieces.
- Sheep's ears may become so edematous they droop from their own weight.
- Sheep may secondarily develop myiasis.
- Sheep and cattle may become chronically ill and die close to parturition.

Lesions

- Hepatocellular degeneration and fibrosis.
- Liver damage is more prevalent than clinical signs.

- Thickening of extrahepatic bile ducts-necrosis of all bile ducts.
- May proceed to biliary cirrhosis with recanalization with new bile ducts.
- Survivors develop large nodules of regeneration and persistent areas of atrophy and fibrosis in liver.

Diagnosis

- Appropriate clinical signs and lesions.
- Common in fall but does occur year round.
- Associated with ryegrass pasture.
- Check with lab as to possibility of analysis.

4. Penicillic Acid

Sources

- Implicated in hepatic cirrhosis in swine.
- Probably not a very significant problem.
- First known mycotoxin-1911.
- Many *Penicillium* spp. produce it.
- Many *Aspergillus* spp. produce it.

Toxicity

- Low toxicity.
    - LD_{50} mice 110 mg/kg SQ.
    - LD_{50} mice 250 mg/kg IV.
    - LD_{50} mice 600 mg/kg Oral.
    - But other reports of LD_{50} as low as 2 mg/kg IP mice.
    - Carcinogen (SQ administration).

Poisonous Plants that Affect the Liver

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Xanthium spp. - Cocklebur

Xanthium strumarium - Common cocklebur
X. orientale - Cocklebur; Sheepbur
X. spinosum - Spiny clotbur

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Herbivores, swine	Hours to days	Days to permanent damage, often lethal	

Family - Compositae (Composite Family)

Description - *Xanthium* spp.

- Plant - rough, coarse, annual, herb 3 feet tall.
- Stem - Erect, stout, widely branched, often red-blotched.
- Leaves - alternate, simple triangular or heart-shaped, rough-toothed or lobed; blades, 6 inches long, broad.
- Flowers - inconspicuous, imperfect.
- Fruit - bur-like, 2-beaked, covered with many spines; 2 compartments, each containing a seed.

Habitat

- Southern Canada, throughout USA, to Mexico.
- In fields, wastelands, flood plains, overgrazed pastures, roadsides.

Toxic Principle

- Carboxyatractyloside, a sulfated glycoside, which is present in high concentrations in the seed and cotyledon, is now thought to be the primary toxic principle.
- Susceptible species.
  - Pigs, cattle, sheep, fowl, horses.
  - Hogs between 20 - 50 pounds appear most susceptible.

Toxicity

- Cockleburs sprout in spring and a dry fall.
- Cotyledonary stages of plant are extremely hazardous to herbivores and omnivores (toxic plus apparently reasonably palatable).
- 0.75% of animal's weight of young seedlings may produce clinical signs of toxicosis in a few hours and death in 24 - 48 hours.
- 500 seedlings are lethal to a 40 pound pig.
- Toxicity is **not** lost on drying.
- Seeds are poisonous, but are contained in a bur and are seldom eaten. Toxic at 0.3% of animal weight. Toxicosis can result when seeds are milled and mixed in feed.

Mechanisms of Action

- Inhibits carrier mediated ADP and ATP transport across mitochondrial membranes.
- Death may occur even when kidney and liver damage are pharmacologically prevented.
- Severe hypoglycemia may occur.
- Burs may cause mechanical damage.

Signs

- General.
    - Appear a few hours to 2 days after ingestion.
    - If death occurs, it is usually within 3 days of the onset of signs.
    - Anorexia, reduced responsiveness.
    - Vomiting, evidence of abdominal pain.
    - Rapid weak pulse, dyspnea.
    - Muscular weakness, prostration.
    - Spasmodic contraction of leg and neck muscles.
- Pig.
    - Evidence of abdominal pain.
    - Opisthotonos, spasmodic running motions, convulsions occur if severely poisoned.
    - Death occurs about 48 hours after onset of signs.
- Cattle.
    - Blindness, extreme hypersensitivity, convulsions are prominent.
    - Calves die acutely within 12 hours.
- Fowl.
    - Pronounced depression, death.

Lesions

- Gastroenteritis, with thickening of the mucosa.
- Hepatic, cardiac and other hemorrhage may be seen.
- Toxic hepatitis with slight icterus is characteristic.
- Ascites may be seen.
- High probability of chronic liver damage.
- Hepatic cirrhosis in recovered animals.
- Renal tubular degeneration (similar to acorn poisoning).

Diagnosis

Identification of *Xanthium*, evidence of consumption and appropriate clinical signs.

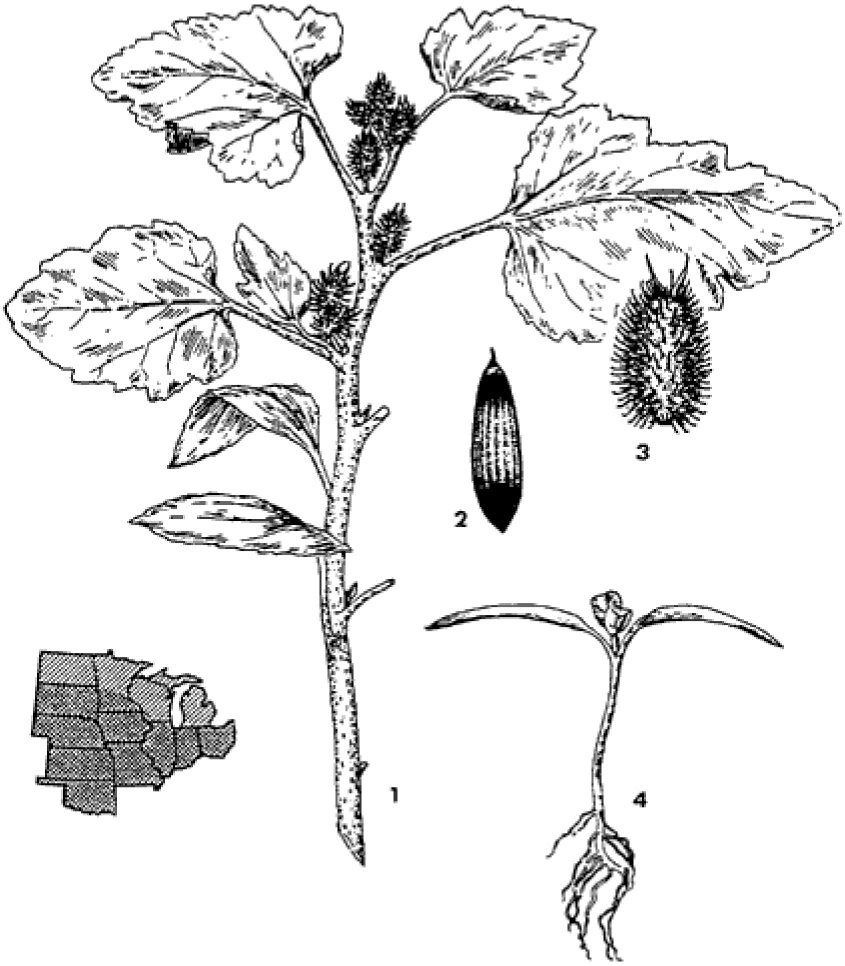
Treatment

- Preferred treatment - Oral activated charcoal (may use dose syringe and administer slurry via nose in swine) - saline cathartic; avoid dehydration.
- Fluids, dextrose, B-vitamins, supportive care.

Prevention

- Remove from source of exposure.
- Control weeds with 2,4-D.

Composite Family, *Compositae*



Common Cocklebur, *Xanthium strumarium* L. - **1**, upper part of plant; **2**, seed; **3**, bur; **4**, seedling plant. **Annual**, reproducing by seed. **Taproot** rather woody, stout. **Stem**, erect, normally bushy, 2 to 4 feet (0.6 to 1.2 m) tall, ridged, rough-hairy, often spotted. **Leaves** alternate, simple, triangular in outline, toothed or lobed, rough, with long petioles. **Flowers** small, male and female flowers separate but borne together in clusters in axils of the upper leaves. Two female flowers are enclosed in each oval bur. At maturity the bur is hard, woody, and covered with hooked prickles, and ends in 2 curved spines. Male flowers numerous, in clusters on short stalks, dropping soon after pollen is shed. **Seeds** about 1/2 inch (1.3 cm) long, dark brown, rather slender with pointed tips. **Found** in cultivated fields, abandoned land, poor pastures, and roadsides.

Senecio - Ragwort-Groundsel

S. jacobaea - Ragwort, stinking Willie, tansy ragwort
S. ridelli - Riddell's groundsel
S. longilobus - Threadleaf groundsel, wooly
S. spartioides - Broom groundsel
S. integerrimus - Lamb's tongue groundsel
S. burchellii
S. douglasii
S. erraticus
S. glabellus
S. ilicifolius
S. lobatus
S. plattensis
S. vulgaris - Common groundsel
S. confusus
S. pauperculus - Prairie groundsel

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal	

Family - Compositae

Description

Senecio spp. Mostly perennial herbs, approximately 3 feet tall. Leaves are palmately dissected, narrow segmentations are present; leaves are whorled, but bracts are not overlapping and form a cup under the head. Flowers are yellow, in heads clustered at the top of the plant and are numerous. The seeds are in both the disc and in the ray florets.

Habitat

- *S. jacobaea* - Europe, now naturalized in Southeast Canada and part of New England. The most serious weed problem in Oregon with estimated yearly losses of $20 million (in Oregon).
- *S. riddellii* - Nebraska to Colorado and New Mexico, West Texas.
- *S. longilobus* - Colorado, Utah to Texas, Arizona and New Mexico.
- *S. spartioides* - Nebraska to Wyoming, south to Texas and Arizona.
- *S. integerrimus* - Minnesota to British Columbia, south to Nebraska and California.
- The western *Senecios* tend to grow in rangelands. *S. jacobaea* grows in roadsides, pastures and waste places. The plants increase in number when pastures are overgrazed.
- *S. vulgaris* is a common weed in hayfields in California and possibly other states. New plantings of alfalfa and alfalfa weakened by heavy weevil infestations are more susceptible to competition by the weeds.
- Oat hay may also be contaminated. These plants are readily identified in baled hay; but it is almost impossible to identify them in hay that is cubed or pelleted.
- *S. pauperculus* - Much of North America except for the southeastern states. In Illinois especially the northern and the western counties; some in east central Illinois.

Toxic Principles

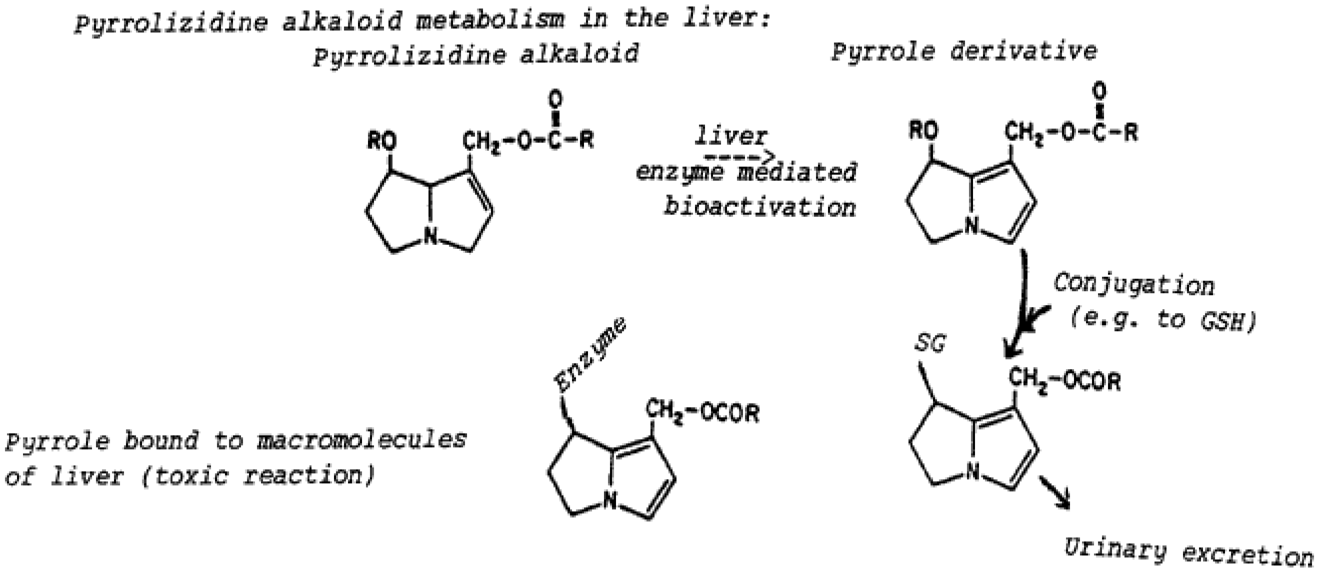
- *S. jacobaea* - Jacobine, jacodine, senecionine.
- *S. ridelli* - Ridelliine.
- *S. longilobus* - Longilobine.
- *S. spartioides* - Seneciphylline.
- *S. integerrimus* - Integerrimine.
- *S. vulgaris* - Senecionine, seneciphylline, retrorsine.
- Of over 100 known pyrrolizidine alkaloids, only a few have proven to be toxic.

Toxicity

- *S. plattensis*is not poisonous. *S. longilobus* (threadleaf groundsel) is eaten throughout the year, especially when the range forage is dry and during ice and snow storms, but stock losses are heaviest in the late spring and summer months.
- Dry leaves retain their toxicity. One to 5% of an animal's weight fed at one time or over a few days may bring on acute toxicosis. 'In the field, acute poisoning is rare, but chronic poisoning is common. In this instance, 12 - 56% of the animal's weight must be eaten before symptoms appear.
- Poisoning tends to occur as a result of ingestion of contaminated hay, at least in the case of common groundsel (*S. vulgaris*) in California. Poisoning may also occur during the growing season when good forage is scarce and the animals are forced to eat these plants.
- In Texas, *S. longilobus* is evergreen and may be eaten in winter. Young leaves are believed to be of greater toxicity than more mature leaves and stems.
- Ensiling hay containing pyrrolizidine alkaloids does not ensure detoxification and multiple deaths have occurred in cattle consuming contaminated silage. However, the addition of molasses to the green chopped plants during the ensiling process may lessen the risk.

Absorption, Distribution, Metabolism and Excretion (ADME) (Applies to All Pyrrolizidine Alkaloid Plants)

Pyrrolizidine alkaloids are rapidly absorbed from the intestine and thereby expose the liver first via the portal circulation. They are also rapidly excreted in body fluids such as milk and urine. Since pyrrolizidine alkaloids are considered to be carcinogens, there is a potential public health problem. In addition, the alkaloids pass across the placenta and can thereby affect the fetus.



Mechanism of Action (Applies to All Pyrrolizidine Alkaloid Plants)

- The toxicity of pyrrolizidine alkaloids is believed to be due to pyrrole derivatives which arise as a result of dehydrogenation of pyrrolizidine alkaloids by hepatic microsomal enzymes. Phenobarbital induction of hepatic enzymes intensifies the hepatotoxicity of pyrrolizidine alkaloids. The activated pyrrole form presumably alkylates macromolecules in the hepatocyte, principally DNA, which impairs cell division.
- In high doses, necrosis of the hepatocytes occurs. More often the metabolic lesion prevents the hepatocyte from undergoing binary fission to regenerate hepatocytes. The cell continues to grow although unable to divide. Both nucleus and cytoplasm expand, sometimes up to 10-fold (hepatocytomegaly and karyomegaly). Ultimately, the cell reaches a critical mass and dies. With mild necrosis, the histopathologic description will be one of parenchymal atrophy with hepatocytomegaly.
- With the death of larger numbers of hepatocytes, the necrosis triggers a regenerative response accompanied by bile duct proliferation. Thus, the 3 primary lesions of pyrrolizidine alkaloid poisoning are hepatocytomegaly (which is always present), fibrosis and bile duct proliferation. The latter 2 lesions are dose and time dependent.
- After chronic ingestion of pyrrolizidine alkaloids, the picture may be one of slow hepatic degeneration, until the hepatic reserve is depleted, at which time liver function collapses and the animal suffers from a generalized hepatic insufficiency syndrome.

Susceptible Species

- Cattle and horses are most often poisoned; sheep and pigs require a longer time to show signs. Although sheep were, at one time, used in reducing the *Senecio* contamination of pastures, they may be poisoned on some strains at doses only slightly higher than those affecting cattle.
- Young, growing animals are more susceptible to the hepatotoxic effects of those compounds than are adults.
- Chronic pyrrolizidine alkaloid poisoning occurs worldwide causing extensive livestock losses.

Signs

- Acute poisoning.
    - Dullness, weakness, abdominal pain and death in a few days to weeks. Horses may exhibit extreme nervous excitement. The acute form is infrequent.
- Chronic poisoning.

  - Clinical signs often may not appear for 2 - 8 months after the first ingestion of pyrrolizidine alkaloids containing plants.
  - Animals lose condition over months and develop icterus. In the later stages, cattle may exhibit nervous derangement and mania. Horses more frequently exhibit nervous signs, especially yawning, drowsiness and staggering. The condition in horses is called "sleepy staggers" and "walking disease". The signs in horses may appear abruptly. Animals may stand apart and lose appetite. An unpleasant, sweetish odor may emanate from the skin. Horses may chew fences and walk aimlessly (off ravines or into buildings, etc.). Head pressing may occur, perhaps due to hepatoencephalopathy. The course often results in death within about a week of onset.
  - Cattle may also exhibit secondary photosensitivity: subcutaneous edema, dry, scaly muzzle. There may also be a rough hair coat, and tenesmus associated with diarrhea or constipation; the straining may result in prolapse. Liver function tests may be worthwhile in subclinical *Senecio* poisoning. In spite of the absence of apparent illness in adult cows consuming pyrrolizidine alkaloids, calf losses may occur.
  - Chronic poisoning of swine is associated with pyrexia and severe respiratory signs.

Gross Lesions

- Acute form.
  - Enlargement and congestion of the liver, necrosis and hemorrhage in lobules.
  - Gastroenteritis.
- Chronic toxicosis.
  - The liver may be enlarged and cirrhotic.
  - Patchy gastroenteritis.
  - Ascites.
- In the horse.
  - Chronic, toxic active hepatitis.
  - Intestinal edema.
  - Enlarged hepatic lymph nodes.
  - Toxic tubular nephrosis.
  - Cerebral edema.
- In swine.
  - Swine experimentally fed *S. jacobaea* for 2 months developed pulmonary edema, congestion and alveolar epithelialization.

Histologic Lesions

- Hepatocytomegaly and karyomegaly.
- Hepatic necrosis.
- Bile duct proliferation.
- Fibrosis and cirrhosis may develop.

Diagnosis

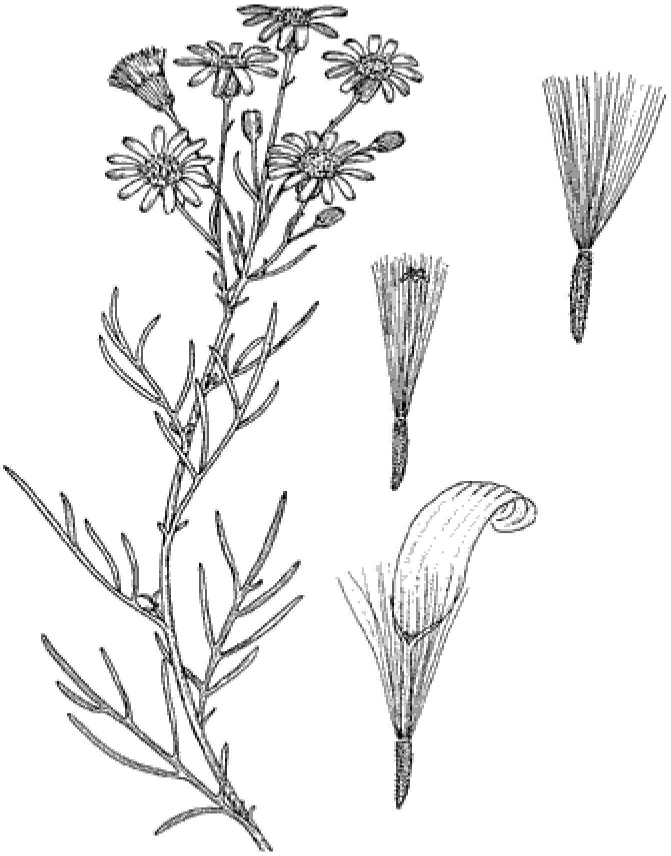
- Sufficient dietary exposure to plant materials.
- Compatible clinical signs and gross as well as histologic lesions.
- Detection of pyrrolizidine alkaloids in plant materials and liver of exposed animals. Contact the USDA Poisonous Plant Research Laboratory in Logan, UT, USA or call 1-801-752-2941.

Treatment

Treatment is usually unsuccessful. Animals should be removed from access to the plant. It has been suggested that laxatives and a high protein, low carbohydrate diet (rationale?) and ensuring adequate fluid intake are beneficial.

Note

As previously mentioned, contaminated hay can serve as the source of pyrrolizidine alkaloids. Due to the prolonged delay in onset of clinical signs and since the affected hay is often no longer available, the likelihood of successful adjudication in the courts is at times quite small.



Threadleaf Groundsel - White wooly stems, showy yellow flowers (enlarged disc and ray flowers, center and lower right), pinnately lobed leaves, and achene fruit (upper right) characterize this unusual shrub.

Crotalaria - Rattlebox

Crotalaria sagittalis - Arrow Crotalaria, rattle box, wild pea
C. spectabilis - Showy Crotalaria
C. retusa
***C. mucronata* var.giant-striate**
C. incana
C. rotundifolia
C. burkeana
C. juncea
C. dura
C. equorum
C. globifera

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal	

Family - *Leguminosae* (Pulse or Bean Family)

Description

- *C. sagittalis*.
  - Plant - Annual to perennial branched herb up to 1.5 feet all.
  - Stem - Conspicuous whitish hairs.
  - Leaves - Simple, oval to linear, 1 - 2 inches long; conspicuous whitish hairs.

    - Flowers - Yellow, inconspicuous, 1/4 inch long.
    - Fruit - Legume pod, 3/4 - 1 inch long, turns black with maturity.
- *C. spectabilis*.
    - Plant - Dense, erect annual to perennial herb up to 6 feet tall.
    - Stem - Never hairy.
    - Leaves - Simple, ovate, dorsally hairless, ventrally covered with fine hairs.
    - Flowers - Yellow, tinged with purple, about 1 inch long.
- *C. retusa*.
    - Plant - Erect, annual herb, not dense, up to 2.5 feet tall.
    - Stems - Very fine hair.
    - Leaves - Simple, narrowly ovate, 2 1/2 - 4 1/2 inches long.
    - Flowers - Yellowish with purple tinge.
    - Fruit - Pod is narrow and up to 1 1/2 inches long.

Habitat

- *C. sagittalis* - Native from Connecticut, south to central Florida, through deep southern states, and into the western part of Illinois, eastern Great Plains, Oklahoma, Eastern Texas. Areas where perennial plants are weak, sandy soil, open areas of blackjack oak woods, extensive stands by Missouri River (cause of Missouri bottom disease of horses).
- *C. spectabilis* - Southern states and as far north as Virginia and Missouri. Roadsides, refuse heaps, farm stands, originally introduced as a soilbuilding, green manure crop, but now naturalized. Seeds are a grain contaminant causing problems in swine and poultry.
- *C. retusa* - Florida Peninsula. Waste areas and along roadsides in sandy soil. Introduced as a soil builder.
- *C. mucronata* - var. *Giant-striata*. Coastal plains of North Carolina. Introduced as soil builder in Southeast

Toxic Principle

- The pyrrolizidine alkaloid, monocrotaline has been identified in *C. spectabilis* and is thought to be in *C. sagittalis*.
- Monocrotaline is a diester of monocrotalic acid and the nitrogen-containing rectroecine.

Mechanism of Action

- Monocrotaline is a pyrrolizidine alkaloid (see Senecio handout), acting on the DNA, especially of hepatocytes, but also has a fundamental action causing constriction of the lumen in the medium and small veins of the hepatic venous tree via subendothelial swelling.
- The plant is pneumotoxic in some areas of the world and mast cells in the lungs of animals fed monocrotaline release 5-hydroxytryptamine which may have some role in the pulmonary vascular lesions.
- The toxic principle of *C. retusa* may be different since characteristic hemorrhage does not occur.

Susceptible Species

- *C. sagitallis* - Horses are more susceptible than cattle.
- *C. spectabilis* - Fowl, cattle, horses and swine are more sensitive than sheep goats and mules.
- *C. retusa* - Fowl are known to be susceptible to several species of *Crotalaria*.

Toxicity

- General.
    - Alkaloid is most concentrated in the seed, but it is also present in the leaves and stem.
    - Also toxic when dry (as in hay).
    - *Crotalaria* turns green early and remains green when other forage turns brown; consequently, most cases of poisoning occurs as a result of ingestion early in spring or late in fall.
- Cattle.
    - Steers fed *Crotalaria* developed clinical signs in 10 days. A total of 55% of the body weight was consumed over 67 days.

    - Nine lb of dried plant killed a 300-lb steer in 4 days.
- Swine.
    - *Crotalaria* fed at 0.05% of body weight produced clinical signs.
    - Two grams of ground seed fed daily produced acute toxicosis in a 50-lb pig in 7 days.
- Fowl.
    - Eighty to 160 seeds produces death in many fowl (30 - 60 days).
    - 0.05% seeds in a ration retards growth.
    - 0.2 lb/ton of seeds in poultry mash interferes with growth.
    - 0.3% seeds in a ration causes 100% mortality within 18 days.
- Horses.
    - *C. sagittalis*.
    - "Bottoms" disease in horses (occurs in horses on low lying areas).
    - One percent of animals body weight of seeds for 2 days produced death on the second day.
    - One quart of pods fed daily produces clinical signs in horses.
- Lab animals.
    - *C. spectabilis*.
    - Most toxic species.
- Poultry.
    - *C. retusa*.
    - One hundred seeds force fed to a white leghorn hen produced death in 1 1/2 - 2 weeks.
    - Ten seeds force fed every day produced death in chickens in 18 - 40 days.
- Lab animals and poultry.
    - *C. mucronata* var. *Giant-striata*.
    - One percent dietary level seriously affects weight gains in Wistar rats.
    - Three to 6% levels in poultry ration causes mortality.
    - Less toxic than *C. spectabilis*.

Signs

- *C. sagittalis* (horses). Bottoms disease.
    - Slow emaciation, weakness, stupor.
    - Fatal in several weeks to months after signs appear.
- *C. spectabilis* (horses).
    - Incoordination, aimless walking and pushing against objects (head pressing) for hours.
    - Delirium, excitement, apparent blindness.
    - Death preceded by icterus, weakness and stupor.
- *C. spectabilis* (cattle).
    - Three syndromes: acute, intermediate, chronic.
    - Acute - Signs appear in 1 day, death in 4 days.
    - Intermediate - Signs appear in 2 months and last 2 - 3 months before death; clinical signs consist of weakness, emaciation, incoordination, constipation or diarrhea.
    - Chronic - Signs develop in a few days or months and consist of loss of appetite, poor condition, tenesmus, nervousness, excitability, blood in feces, prostration, bloody nasal discharge and death.
- *C. spectabilis* (swine).
    - Signs appear in several weeks.
    - Loss of hair, unthriftiness.
- *C. spectabilis* (fowl).
    - Characteristic comb discoloration in 29 hours.
    - Severe greenish-yellow diarrhea.
    - Birds are depressed, ruffled feathers.
- *C. retusa*.
    - Clinical signs are similar to *C. spectabilis* but are less acute and with much less hemorrhage.
- *C. mucrorata* var. **Giant-striata**.
    - Causes retardation of weight gain in chickens and rats, and probably other animals.

Gross Lesions

- *C. sagittalis*
    - Congestion and hemorrhage.
    - Degeneration of liver and spleen.

    - Stomach is abnormally full of undigested food.
- *C. spectabilis* (cattle).
    - Acute - Profuse hemorrhage on the serous membranes of the abdominal and thoracic cavities.
    - Intermediate - Hepatic cirrhosis, ascites, petechiae on the intestinal serosa.
    - Chronic - Widespread hemorrhage, petechiae or ecchymoses in nearly all tissues; ascites, edema in the mesenteries, occasional icterus; degeneration of parenchymatous organs, liver indurated and bluish-gray.
- *C. spectabilis* (swine).
    - Anemia, ascites.
    - Firm indurated liver.
    - Hemorrhages of heart.
    - Gastritis.
- *C. spectabilis* (fowl).
    - Odor of crushed leaves in carcass.
    - Dehydration, full crop.
    - Thickened air sacs and pericardial sacs.
    - Atrophic spleen.
    - Petechial hemorrhages of serous membranes of abdominal and thoracic cavities.
    - Petechial and suffusive hemorrhage of the visceral fat, heart and musculature.
    - Swollen kidneys.
    - Dark, small, marbled liver.
    - Liver may be ruptured.
    - Enlarged gallbladder.
    - Distended abdomen due to ascites.
- *C. mucronata* var. *Giant-Striata* (fowl).
    - Almost entirely limited to liver.
    - Fibrous thickening of liver capsules with or without edema.

Histologic Lesions

See Histologic Lesions section for *Senecio*.

Diagnosis

See Diagnosis section for *Senecio*.

Treatment

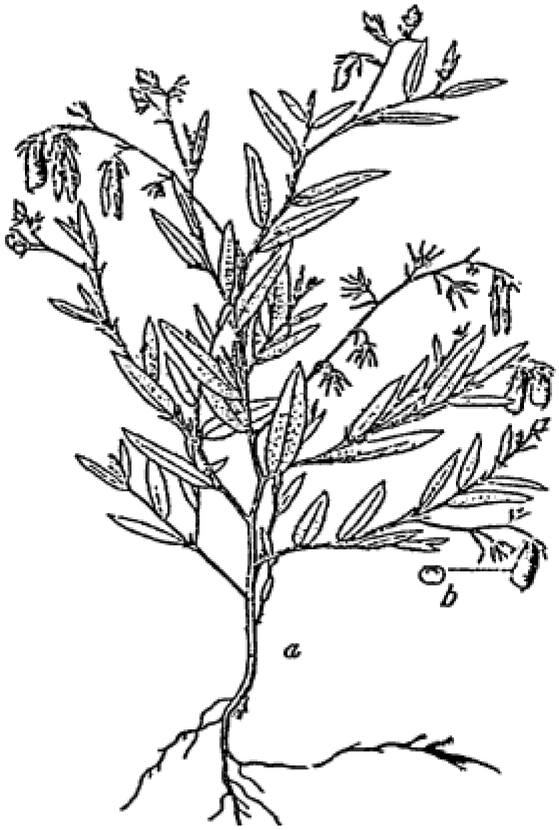
- Treatment has little value after signs appear.
- Protectants, blood transfusions and fluid therapy may be attempted.
- Symptomatic therapy may prolong life.

Prevention

Avoid grain contaminated by all *Crotalaria* species.

Comments

- *C. intermedia* has been shown to be non-toxic.
- *Crotalaria* spp. causes many problems in Australia.
- *Crotalaria* is an excellent green-manure plant.
- Modern harvesting of corn and other crops may result in the contamination of stains with *Crotalaria* seed.
- Spraying of pasture and crop land with broad-leaf killing herbicides has largely eliminated *Crotalaria* poisoning in the continental United States for the present.



Rattlebox (*Crotalaria sagittalis*) - **a**, whole plant; **b,** cross section of seed pod - both one-third natural size.

Amsinckia - Fiddleneck

Amsinckia intermedia - Tarweed, fingerweed, fiddlenecks, fireweed

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Herbivores, cattle, horses, pigs, poultry; sheep less susceptibleDays to weeks	Days to permanent damage; often lethal		

Family - Boraginaceae (Borage Family)

Description

- *A. intermedia*
    - Plant - Erect, annual, covered with numerous white bristly hairs, 13 feet tall.
    - Stem - Sparsely branched.
    - Leaves - Alternate, hairy, lanceolate-linear, thick, covered with bristly hairs.
    - Flowers - Inflorescence dense, 1-sided, coiled.
    - Fruit - 2 - 4 gray-black nutlets, about 2.5 mm long, small, long, ovoid, angular, rough.
- Native to Pacific Coastal states; spreading eastward locally.
- California, Oregon, Washington, Idaho.
- Grain fields, gardens, orchards, waste places, of semiarid regions, dry open cultivated ground; wheat screenings used to fatten animals.
- Frequently encountered as a weed in hayfields.

Toxic Principle

- Pyrrolizidine alkaloid (see *Senecio*).
- Nitrates may accumulate to potentially lethal concentrations.

Toxicity

- General.
  - Screenings from wheat contaminated with tarweed is toxic.
  - Lambs tolerated 25% nutlets mixed with wheat grain for 125 days.
  - Toxic effects appear to be cumulative.
  - Five percent *Amsinckia* seeds in diet, produced death of a pig in 2 months.
  - Leaves are also toxic.
  - Large amounts of seeds may cause death in a short time.
  - Sheep, lambs, mules and fowl are more resistant to poisoning.
- Chronic.
  - After ingesting small amounts over a long period, animals will fail to gain weight and lose condition.

Signs

- Hemorrhage of the gastrointestinal tract and subcutaneous tissues.
- Unthriftiness, icterus, sluggishness, sleepiness.
- Delirium, aimless wandering.
- Anemia, failure to gain weight.
- Small ulcers on lip and gum mucosa with offensive odor.
- Horses.
  - "Walking Disease"
  - Sluggishness, sleepiness, furious delirium or aimless walking.
  - Small ulcers on mucosae of lips and gums accompanied by offensive odor.
  - Anemia may develop in later stages.
- Swine.
  - "Hard Liver Disease"
  - Failure to gain weight between 30 - 100 lb. Animals become long and narrow, head may appear to elongate due to muscle atrophy.
  - Appearance may be similar to severe parasitism.
  - Unthriftiness, icterus.
- Cattle.
  - "Hard Liver Disease".
  - Unthriftiness, icterus.
  - Poor condition.

Lesions

- Hepatic cirrhosis.
- Hemorrhage in the subcutaneous tissue or in the gastrointestinal tract.
- Primarily a hepatotoxic problem. Pigs and rarely, sheep and cattle may also develop renal megalocytosis.
- See Histologic Lesions section for *Senecio*.

Diagnosis

See Diagnosis section for *Senecio*.

***Amsinkia*. Fiddleneck.**

Echium spp.

Echium vulgare - Blue thistle, blue devil, viper's bugloss
E. plantagineum - Paterson's curse, salvation Jane

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal	

Family - Boraginacea (Borage Family)

Description

- *Echium* spp.
    - Plant - Rough, hairy, herb.
    - Leaves - Alternate, entire.
    - Flowers - Symmetrical, 4-lobed, single style; 5-parted calyx.
    - Fruit - 4 - 1 seeded nutlets or 2 - 2 seeded nutlets.

Habitat

- *E. vulgare* - Northeastern USA (East of Mississippi).
- *E. plantagineum* - Southern states. Dry meadows and pastures; limestone regions.

Poisonous Principle

Pyrrolizidine alkaloids (see *Senecio*).

Susceptible Species

Sheep, cattle, horses, pigs.

Toxicity

- General.
    - Contact with bristly hairs on the leaves or stem may produce dermatitis.
    - All parts toxic.

Clinical Signs

- General.
    - Dermatitis, itching.
    - Hepatoses.

Lesions

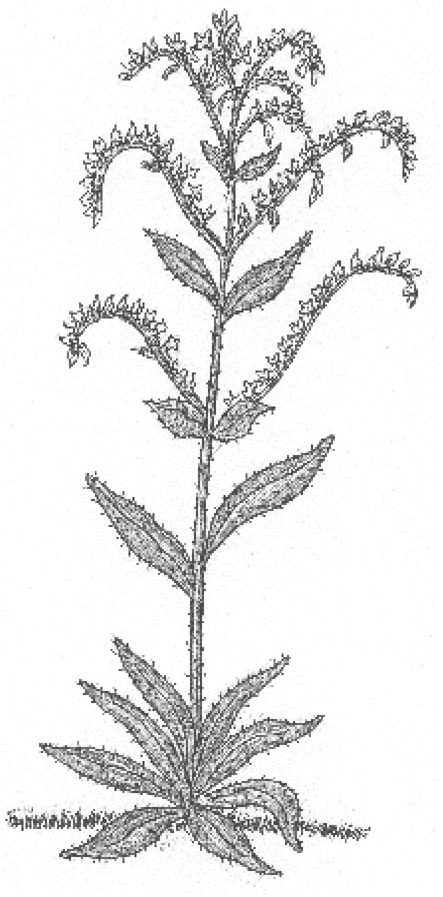
- See Histologic Lesions, section on *Senecio*.
- Hepatotoxic.
- Pigs and rarely sheep and cattle develop renal megalocytosis.
- Laboratory animals develop pulmonary disease.

Diagnosis

See Diagnosis, section on *Senecio*.

Prevention

- Carefully control by grazing with closely observed, less valuable sheep (they are somewhat resistant).
- Supplemental feed.



Echium

Heliotropium (Heliotrope)

Heliotropium europaeum - Heliotrope

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal	

Family - Boraginaceae

Description

An annual weed (do not confuse with *Valeriana officinalis*, the garden heliotrope).

Habitat

The plant occurs rather sparingly in the southeastern states from Florida up to New Jersey and occasionally into New England; most problems have been reported in Australia.

Toxic Principle

- Two alkaloids of pyrrolizidine type; heliotrine and lassiocarpine, and their respective N-oxides.
- Allylic esters of pyrrolizidine alkaloids which are also hepatotoxic.
- Plant may contain up to 3% alkaloids, mostly as N-oxides.

Toxicity

- General.
    - No known losses in USA.
    - Toxicosis results from ingestion of a large quantity over an extended period.

Absorption, Distribution, Metabolism and Excretion (ADME)

- The N-oxides of the alkaloids are more soluble and therefore absorbed rapidly, intact; whereas the parent alkaloids are significantly degraded in the rumen.
- Metabolism to the much more toxic pyrrole compounds occurs in the tissues after absorption.

Mechanisms of Action

- Pyrrolizidine alkaloid (see *Senecio* handout).
- Slow acting liver toxin, sometimes with a high death rate.
- In most cases, animals can consume large amounts over an entire season without developing signs. However, the hepatocyte changes persist and predispose the affected animal to serious poisoning the second season.

Signs

- General.
    - Progressive loss of condition characteristic of liver atrophy.
    - Perhaps photosensitization.
    - Hemolytic jaundice (sudden) - high copper content of some plants is associated with this type of jaundice.
    - Death.

Lesions

Liver damage (atrophic hepatosis).

Diagnosis

Identification of *Heliotropium*, evidence of consumption, and appropriate clinical signs and lesions.

Treatment

- Remove animal from source of plant.
- Evidence suggests that cobalt may facilitate the detoxification of pyrrolizidine alkaloids via vitamin B_{12} before liver damage occurs.

Prevention

- Sheep have been used in Australia to graze infested areas during seedling stages.
- Supply ample cobalt to form vitamin B_{12} which may help to limit pyrrolizidine alkaloid effects.

Microcystis Aeruginosa, M. Viridis, Anabaena Flos-Aquae, Nostoc* spp.,*Oscillatoria Aghardii*, and *Nodularia Spumigena

Hepatotoxic Blue-Green Algae

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
All species	Hours (usually) to chronic	Days to permanent damage; highly lethal	

Habitat

- Potentially toxic blooms of *Microcystis aeruginosa*, *Anabaena flos-aquae*, *Nostoc* spp., and *Oscillatoria aghardii* occur during sunny weather in stagnant bodies of freshwater with high nutrient (especially phosphate) concentrations, such as occur in eutrophic ponds, lakes, and reservoirs. Commonly animals are exposed to potentially toxic amounts when pastures or holding pens uphill have fertilized the pond with animal wastes and wind has concentrated the bloom near the side of the pond where the animals drink.
- *Nodularia* blooms occur in brackish water. Problems have been documented especially in Australia and the Baltic Sea.
- Microcystins have also been shown to cause liver failure in fish raised in net pens in marine coastal areas. The source of these microcystins is unknown, but nutrient enrichment associated with fish food and excreta may encourage algal growth.
- Microcystins from a reservoir in Brazil were present in water used in dialyze a number of kidney patients. Liver failure occurred as well as several deaths.
- Shrimp are relatively tolerant of microcystins and may bioaccumulate potentially toxic amounts.

Description

- Blue-green algae cells in water are green, blue-green or blue depending on their degree of deterioration. Fresh blooms are green, and the colonies of cells are approximately the size of grains of sand and often float at or near the surface of the water. Microscopically, colonies of *Microcystis* (Fig. 1) cells contain hundreds or thousands of marble-like cells grouped in a common mucilaginous matrix. Colony shape may be round or irregular. The individual cells are approximately the size of erythrocytes.
- Microscopically, *Noduria* are more linear (Fig. 2) as are *Oscillatoria* (not shown) and *Anabaena* .

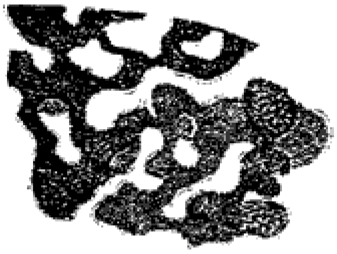


Figure 1 - *Microcystis aeruginosa*.

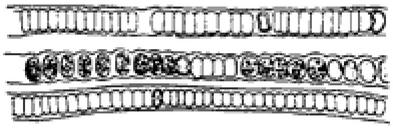


Figure 2 - *Nodularia spumigena*.

Toxic Principle

- Microcystins and nodularin are a group of similar cyclic peptides containing some very unusual residues (not all are amino acids of a structure common to animals), that are responsible for the hepatotoxic properties of *Microcystis* and *Nodularia*. In the older literature the microcystins were termed "fast-death factor".
- Blue-green algae also have lipopolysaccharide endotoxins in their cell walls.
- Most toxic strains of *Anabaena* and some toxic strains of *Oscillatoria* and *Microcystis* contain neurotoxins.

Mechanism of Action

- Hepatocytes are the primary target cell in liver.
- Specificity for hepatocytes is related to cell uptake of the toxins via bile acid carriers.
- The biochemical mechanism(s) of action of microcystins and nodularin is inhibition of protein phosphatases 1 and 2A; which results in excessive phosphorylation of specific intracellular proteins including cytokeratins 8 and 18 which are the major proteins in cytoskeletal intermediate filaments of hepatocytes.
- The hepatocytes round-up apparently due to a loss of the normal arrangement of intermediate filaments, microtubules, and actin microfilaments, the three major components of the hepatocyte cytoskeleton. The hepatic sinusoids are severely disrupted. The resultant intrahepatic hemorrhage and necrosis, as well as acute hepatic insufficiency, possibly accompanied by hypoglycemia, may result in severe circulatory shock and death.

- Toxicoses may be aggravated by endotoxins, but this has not been well documented at this time.

Signs

- Animals ingesting toxic amounts of *Microcystis* blooms often develop an acutely lethal syndrome characterized by gastrointestinal disturbances (vomiting depending on species, abdominal pain and often diarrhea which may be bloody), followed by weakness, pallor of the mucous membranes, severe reduction in both activity and responsiveness, and death.
- The syndrome often lasts less than 24 hours from the onset until death.
- It is also possible to have sublethal toxicoses with substantial liver damage but most animals not lethally exposed often seem to make a successful recovery. The area of sublethal toxicosis does, however, need further characterization.
- Secondary (hepatogenous) photosensitization sometimes develops in surviving herbivores.

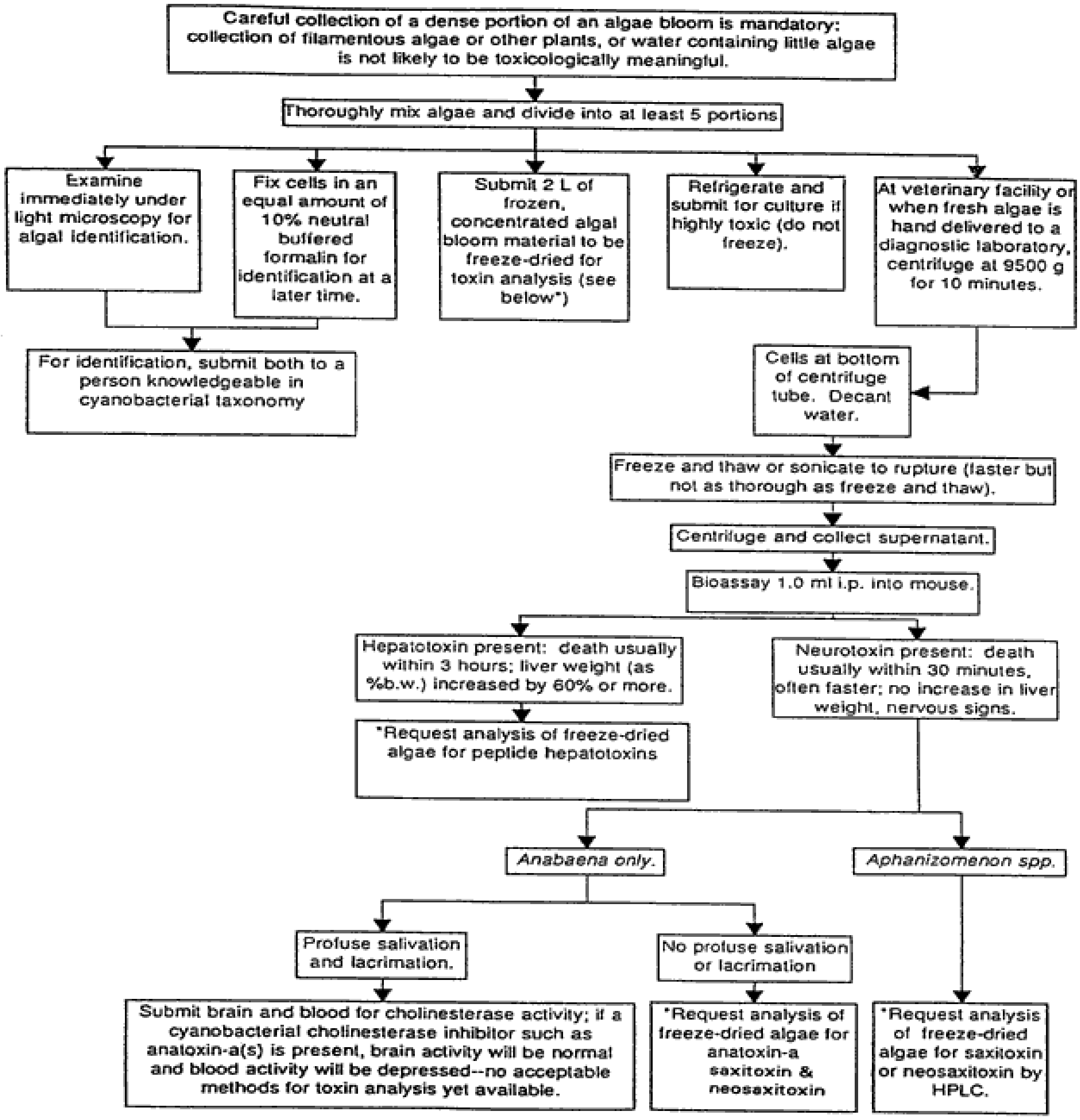
Lesions

- The liver tends to be swollen and to contain abnormal amounts of blood.
- Often the lobular pattern may be exaggerated (depending on species) due to hemorrhage into the liver lobules. There may be significant edema in and around the wall of the gallbladder.
- Microscopically, the picture is one of acute separation of hepatocytes from one another, toxic centrilobular apoptosis followed in some cells by necrosis which may extend nearly to the entire liver lobule with replacement by hemorrhage.
- In time-course studies, intact hepatocytes and especially hepatocyte debris are evident in the central veins of the damaged liver. These can be observed even in pulmonary capillaries. At death, however, only granular debris may remain.
- Marked edema of the gall bladder may be evident.
- Secondary (hepatogenous) photosensitization due to blue-green algae has been documented in cases from the field.

Diagnosis

- Diagnoses are based on history, and appropriate clinical signs, gross and microscopic lesions, and identification of the algae in the water.
- Blue-green algae should be collected from a suspected source soon after the incident, so that human efforts to kill out the bloom or changes in wind direction or weather are not able to remove it before identification.
- One portion of the sample should be immediately examined microscopically to find the colonies of algal cells.
- A 1 ml specimen of cells should be shipped chilled (not frozen) to a laboratory capable of culturing the cells as rapidly as possible. Contact Dr. Val Beasley of the College of Veterinary Medicine, University of Illinois, 2001 S. Lincoln Avenue, Urbana, IL 61801, USA or Dr. Wayne Carmichael, Department of Biological Science, Wright State University, Dayton, OH 45435, USA.
- A gallon of the concentrated algal cell material should be frozen and shipped for toxin analysis.
- A smaller specimen (5 ml) should be combined with an equal amount of buffered, neutral 10% formalin in order to fix the algae and prevent its physical deterioration.
- The gastrointestinal tract contents of lethally poisoned animals may also contain the readily identifiable colonies of *Microcystis* cells.

Diagnostic Flow Chart for Suspected Blue-Green Algae Cases


Careful collection of a dense portion of an algae bloom is mandatory: collection of filamentous algae or other plants, or water containing little algae is not likely to be toxicologically meaningful.
Thoroughly mix algae and divide into at least 5 portions
Examine immediately under light microscopy for algal identification.
Fix cells in an equal amount of 10% neutral buffered formalin for identification at a later time.
Submit 2 L of frozen, concentrated algal bloom material to be freeze-dried for toxin analysis (see below*)
Refrigerate and submit for culture if highly toxic (do not freeze).
At veterinary facility or when fresh algae is hand delivered to a diagnostic laboratory, centrifuge at 9500 g for 10 minutes.
For identification, submit both to a person knowledgeable in cyanobacterial taxonomy
Cells at bottom of centrifuge tube. Decant water.
Freeze and thaw or sonicate to rupture (faster but not as thorough as freeze and thaw).
Centrifuge and collect supernatant.
Bioassay 1.0 ml i.p. into mouse.
Hepatotoxin present: death usually within 3 hours; liver weight (as %b.w.) increased by 60% or more.
Neurotoxin present: death usually within 30 minutes, often faster; no increase in liver weight, nervous signs.
*Request analysis of freeze-dried algae for peptide hepatotoxins
Anabaena only.
Aphanizomenon spp.
Profuse salivation and lacrimation.
No profuse salivation or lacrimation
Submit brain and blood for cholinesterase activity; if a cyanobacterial cholinesterase inhibitor such as anatoxin-a(s) is present, brain activity will be normal and blood activity will be depressed--no acceptable methods for toxin analysis yet available.
*Request analysis of freeze-dried algae for anatoxin-a saxitoxin & neosaxitoxin
*Request analysis of freeze-dried algae for saxitoxin or neosaxitoxin by HPLC.

Treatment

- No specific treatment for microcystin or nodularin toxicosis has been explored.
- Animals recently exposed should have measures taken to thoroughly evacuate their gastrointestinal tracts at the earliest possible time, and should be given activated charcoal and a saline cathartic. In small animals, cholestyramine, if immediately available, would be preferred over activated charcoal.
- Steps to combat hemorrhagic shock are indicated, such as intravenous fluids and possibly blood transfusions, corticosteroids, and, if marked metabolic acidosis is present, sodium bicarbonate should be given slowly IV (in fluids).

Note

- Some species and strains of *Anabaena* produce microcystin-LR and/or other microcystins. Generally the same clinical effects would be expected and diagnostic and therapeutic approaches followed. However, *Anabaena*-associated hepatotoxicosis has not been documented often in cases from the field.

- Recently, a structurally-unrelated (cyclic guanine derivative) algal hepatoxin, termed cylindrospermopsin from *Cylindrospermosis raciborskii* has been identified. It seems to have caused liver failure in human beings. It's action is to interfere with synthesis of glutathion.

Lantana and *Lippia* spp.

Lantana camara - Largeleaf Lantana
L. involucrata
L. aculeata
L. ovalifolia
L. sellowiana
Lippia ligustrina - White brush

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Poisonous Plants that Affect the Liver
Herbivores	Days to chronic	Weeks to permanent damage; often lethal	

Family - Verbenaceae (Verbena Family)

Description

- *Lantana* spp.
  - Plant - Erect or spreading shrub.
  - Stem - Ridged, angular, prickly.
  - Leaves - Opposite, ovate, crenated or serrated margin, veined from base, spreading hairs, 1.5 - 5 inches long.
  - Flowers - Small, tubular, spreading lobes, long axillary peduncles, yellow or pink changing to orange or bright red.
  - Fruit - Fleshy, drupe-like, 2-celled or 2 one-seeded.
- *L. camara*
  - Plant - Low, perennial shrub, 3 - 6 ft tall.
  - Stem - Square, sparse weak spines, occasionally vine-like, hairy.
  - Leaves - Opposite or in whorls of 3, ovate, petioled, crenatedentate, 2 - 4 inches long, 1.2 - 2.4 inches wide, toothed, aromatic, rough above, hairy beneath; leaf stalks, 0.4 - 0.8 inches long.
  - Flowers - Small, tubular, yellow or pink changing to bright red, 0.4 - 0.5 inches long, 0.24 - 0.31 inches across; in flat-topped clusters, axillary umbels, 1.6 - 2.4 inches across.
  - Fruit - Greenish-blue or black, fleshy, berry-like, 0.24 - 0.31 inches diameter, glossy; seeds, oval, 0.16 - 0.2 inches long, 0.12 - 0.14 inches thick, grooved on 2 sides, brown, rough, irregular.
- *Lippia liqustrina*
  - Plant - Shrub, often spiny, 0.4-1.2 ft high.
  - Leaves - Opposite, lanceolate to oblong, veinless, 0.2-1 inch long.
  - Flowers - In slender, naked spikes.
  - Fruit - 2-celled nutlets; 1 seed per cell nutlets, greenish-blue or black 1/4 inch in diameter.

Habitat

- General - Southern Africa; Australia; India.
  - *L. camara* - Central and Southern Florida; Northern USA and Canada as an ornamental; Australia; Mexico.
  - Fence rows, ditch banks, fields, waste areas, pastures, sandy soils, potted; cultivated as outdoor annual, dry woods.
  - *Lippia* spp. - Southwest Texas to Mexico
  - Also grown as a potted plant in Central and other parts of USA.

Toxic Principle

- Pentacyclic triterpene acids, including lantadene A and B, reduced lantadene A, dihydrolantadene A, and icterogenin.
- Hepatogenous photosensitizer.
- Gastrointestinal irritants.

Susceptible Species

- *Lantana camara* - Sheep, cattle, children.
- *Lippia* spp. - Cattle, sheep, goats, horses.

Toxicity

- *Lantana camara*.
    - Foliage and ripe berries contain toxic substance.
    - Green berries have a higher concentration of the toxin.
    - Berries may be lethal to children. However, some dark skinned people eat ripe berries without noticing ill effects.
    - Lantana is one of the main causes of poisoning in Florida.
    - Three-fourths to 1 lb of dry leaves may cause toxicosis of a 400 lb bovine (1% of animals weight) (green weight basis).
    - Two percent of sheep's weight produced fatal results in 5 days.
    - Toxicity of individual plants is genetically determined.
    - Fifty to 90% of animals newly exposed are affected.
    - High mortality of affected animals (90%).
    - All species of *Lantana* should be considered poisonous.
    - Poisoning commonly occurs among grazing animals.
- *Lantadene A.*
    - One dose of lantadene A, 1 - 3 mg/kg, produces mild liver injury, increased SGOT and SDH; but serum bilirubin does not increase.
    - One dose at 3 mg/kg or 7 doses at 1 mg/kg over 3 days causes cholestasis, elevated SGOT, SDH, and bilirubin; green discoloration of the liver; enlarged gallbladder; dry impacted feces may be found in rectum; renal tubular necrosis.
    - One dose of 4 - 8 mg/kg causes centrilobular, midzonal, and massive hepatic necrosis; hemorrhage into the intestinal tract is common.
    - One dose at 60 mg/kg given orally is toxic to sheep.

Mechanism of Action

- Hepatogenic photosensitizer; hepatotoxic; cholestasis.
- The toxins have effects on both hepatocytes and bile canaliculi.
- Decrease in canaliculi ATPase activity.
- Collapse of canaliculi.
- Secretory function of hepatocytes is lost; metabolizing function is retained.
- Literature is in disagreement as to whether or not normal bilirubin conjugation is retained.

Signs

- **Lantana**.
    - Acute toxicosis:
        - The major clinical effect of *Lantana* toxicosis is photosensitization, the onset of which often takes place in 1 to 2 days after consumption of a toxic dose (1% or more of animal's body weight).
        - Jaundice is usually prominent, animals usually become inappetent, and they often exhibit decreased digestive tract motility and constipation.
        - Other signs may include: sluggishness, weakness, and transient, sometimes bloody diarrhea. In acute cases, death occurs in 2 to 4 days.
    - Subacute and chronic toxicosis:
        - Subacute poisoning is more common.

        - Raw photosensitized surface areas are susceptible to invasions by blow fly maggots and bacteria.
        - In severely affected cattle, lesions may appear at the muzzle, mouth, and nostrils.
        - Ulceration may be present in the cheeks, tongue, and gums, while swelling, hardening, peeling of mucous membranes, and deeper tissues occur in the nostrils.
        - Death may occur after 1 to 3 weeks of illness and weight loss.
- *Lippia* spp.
    - Emaciation.
    - Leg weakness.
    - Incoordination.

Lesions

- General.
    - Highly pigmented liver.
    - Icterus, general edema.
    - Gallbladder paralysis and distention.
    - Necrosis of renal tubules.
    - Hemorrhages in some organs.
    - Myocardial damage and intestinal paralysis has been suggested, but conclusive supportive evidence is lacking.
- Cattle (severe cases).
    - Lesions from muzzle to mouth and nostrils, ulceration of cheeks, tongue, and gums.
    - Swelling, hardening, peeling of mucous membranes and deeper tissues in the nostrils.
- Human.
    - Acute pulmonary edema and "neurocirculatory collapse" has been reported in a 2 1/2 year old girl.

Diagnosis

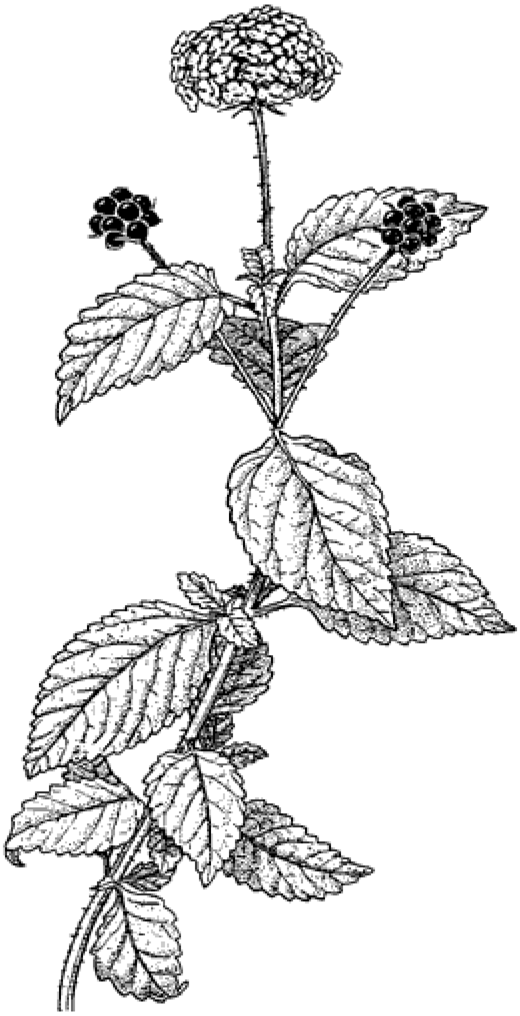
Identification of *Lantana* or *Lippia*, evidence of consumption and appropriate clinical signs and lesions (browsing might be overlooked because of the small amount necessary to cause toxicosis).

Treatment

- Treat for 12 -24 hours to overcome reduction in gut motility.
- Physostigmine may initiate dramatic reversal of some of the signs within minutes.
- Contraindications for the use of physostigmine include: asthma, gangrene, cardiovascular disease, mechanical obstruction of the gastrointestinal or urogenital tracts.

Prevention

- Grubbing and destruction of plants is most practical.
- Herbicides.



Lantana - The oval, toothed, and veiny leaves; the square prickly stems; the terminal flower clusters; and the black berries are characteristic of this attractive ornamental shrub.

Helenium spp. - Sneezeweeds

H. autumnale - Common or autumn sneezeweed, staggerwort, swamp sunflower
H. hoopesei - Orange or western sneezeweed, yellowweed
H. microcephalum - Small head sneezeweed
H. nudiflorum - Purplehead sneezeweed
H. tenuifolium - Bitter sneezeweed, bitterweed, fennel

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Esp. sheep and goats, cattle, horses, swine, rabbits	Hours to chronic	Days to weeks; often lethal	

Family - Compositae (Composite or Sunflower Family)

Description

- *H. autumnale* - Perennial, lanceolate leaves of equal size, flowers yellow, rays reflexed.
- *H. hoopesei* - Perennial; oblong/lanceolate leaves, smaller on the upper stem; flowers are orange-yellow, with large horizontal rays. Twenty to 40 inches tall.
- *H. microcephalum* - Annual, lanceolate leaves; numerous flower heads with yellow rays.

- *H. nudiflorum* - Perennial; linear to lanceolate leaves which are golden-yellow; rays may have a purplish base, not reflexed.
- *H. tenuifolium* - Annual; 6 - 30 inches high; linear leave, yellow flowers.

Habitat

- *H. autumnale* - Eastern North America, wet pastures, meadows, ditches, near streams.
- *H. hoopeseii* - Western Montana to eastern oregon southward to California and New Mexico (5,000 - 12,000 feet elevation). Moist slopes and well- drained mountain meadows in high ranges.
- *H. microcephalum* - Southern Texas and Mexico. Moist ground, most toxic at flowering.
- *H. nudiflorum* - Eastern USA to Michigan and Texas. Wet pastures, meadows, ditches, along streams.
- *H. tenuifolium* - Southeastern USA to Texas. Sandy fields, woods, waste areas.

Toxic Principle

- Helenalin; helenanolide, tenulin sesquiterpene lactones. Helanin is believed to be the primary toxic constituent.
- The glycoside dugaldin.

Mechanism of Action

The effect of helanin is believed to be similar to that of hymenoxon (see handout on *Hymenoxys*).

Susceptible Species

Sheep and goats are more susceptible than horses, cattle and rabbits.

Toxicity

- All parts are toxic, especially the leaves and flowers.
- Poisoning is common in the late summer or fall when other forage is scarce.
- Among the most dangerous range plants to livestock.
- Also unsafe for human consumption.
- Stable toxic principle, resists drying.
- Toxicity of plants varies greatly.
- Somewhat cumulative effects.
- One percent of an animal's weight for 8 days may produce severe illness and death.
- Many species remain green even when covered with snow.
- *H. hoopeseii* - Causes trouble in spring since it is green before other forage.
- *H. microcephalum* - 0.25% of sheep's body weight was rapidly fatal.
- 2.5 gm/kg of body weight may cause acute poisoning and death in cattle.
- *H. tenuifolium* - Bitter, sharp taste, but occasionally grazed in quantity, when more palatable foliage is scarce.
- Sneezeweed poisoning (spewing sickness) is more of a problem in sheep than in other species.

Signs

- Acute Syndrome.
    - Depression, decreased appetite, ruminal atony, mild tympany.
    - Arched back, grinding of teeth.
    - Serous nasal discharge, slight evidence of regurgitation.
    - Excessive salivation, bloating.
    - Severe abdominal pain.
    - Vomition and diarrhea.
    - Head pushing occurs terminally.
    - Apparently agonal seizures.
    - Recumbency with clonic and tonic convulsions.
    - Death within 4 - 24 hours after consumption.
- Chronic syndrome.
    - Several weeks of ingestion are required before signs appear (in the chronic syndrome).

    - Weakness and salivation as well as diarrhea and a febrile response may appear.
    - Vomiting is characteristic in sheep, and therefore a green nasal discharge is present and these signs give rise to the name spewing sickness.
    - Loss of muscular control has been suggested.
    - Death occurs with or without agonal spasms.
    - Milk may have a bitter taste.
    - Photosensitization may occur.

Lesions

- *H. microcephalum*.
    - Serosanguinous fluids accumulate in all body cavities.
    - Tubular nephrosis may be seen.
- *H. hoopeseii*.
    - Liver degeneration.
- General.
    - A gastrointestinal irritation.
    - Hepatic and renal congestion.
    - Gastric edema.
    - Adhesion of necrotic areas of the lungs; probably a result of aspiration pneumonia.
    - Endocardial hemorrhage, pulmonary edema, fluid in pleural cavity, ascites.
    - Elevated serum transaminase activities, result of hepatic necrosis.
    - Renal damage.

Diagnosis

- Identification of sneezeweed.
- Evidence of consumption in sufficient quantities.
- Appropriate clinical signs and lesions.

Treatment

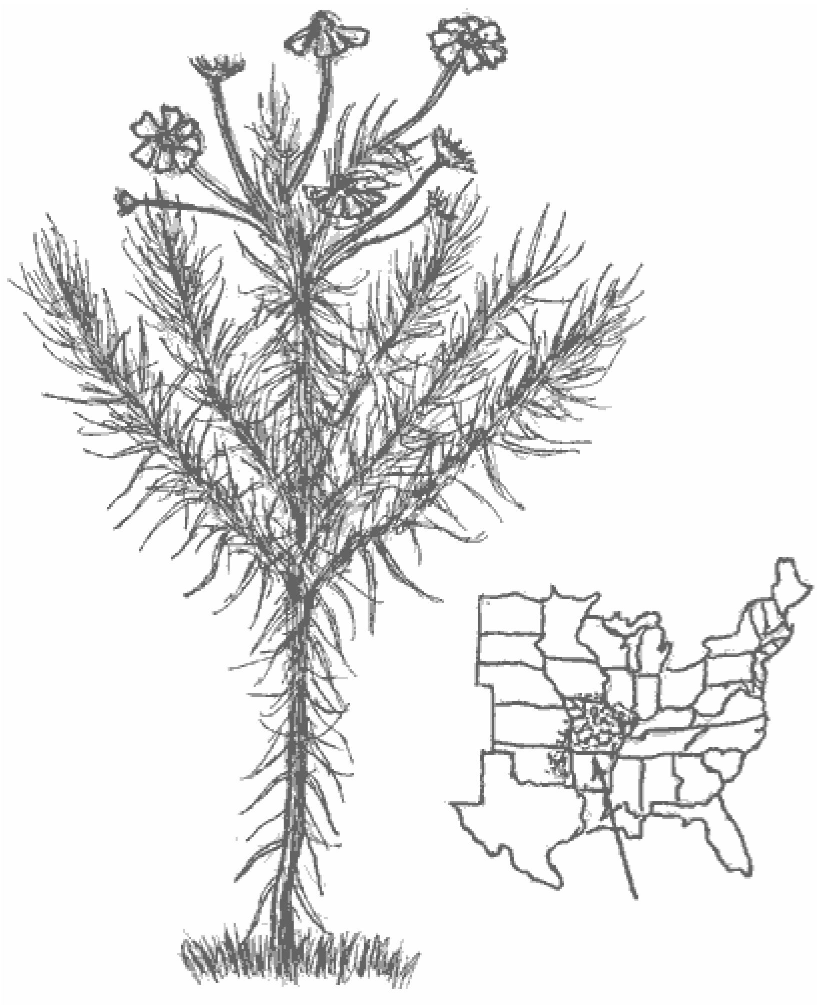
- Remove animals from access to the plant.
- The oral administration of lard and other oils, before the onset of spasms has been recommended.
- Administration of L-cysteine before clinical signs appear has been suggested.
- Activated charcoal and a saline cathartic are likely to be of benefit if animals have very recent exposure (hours) to a large amount of the plant.

Prevention

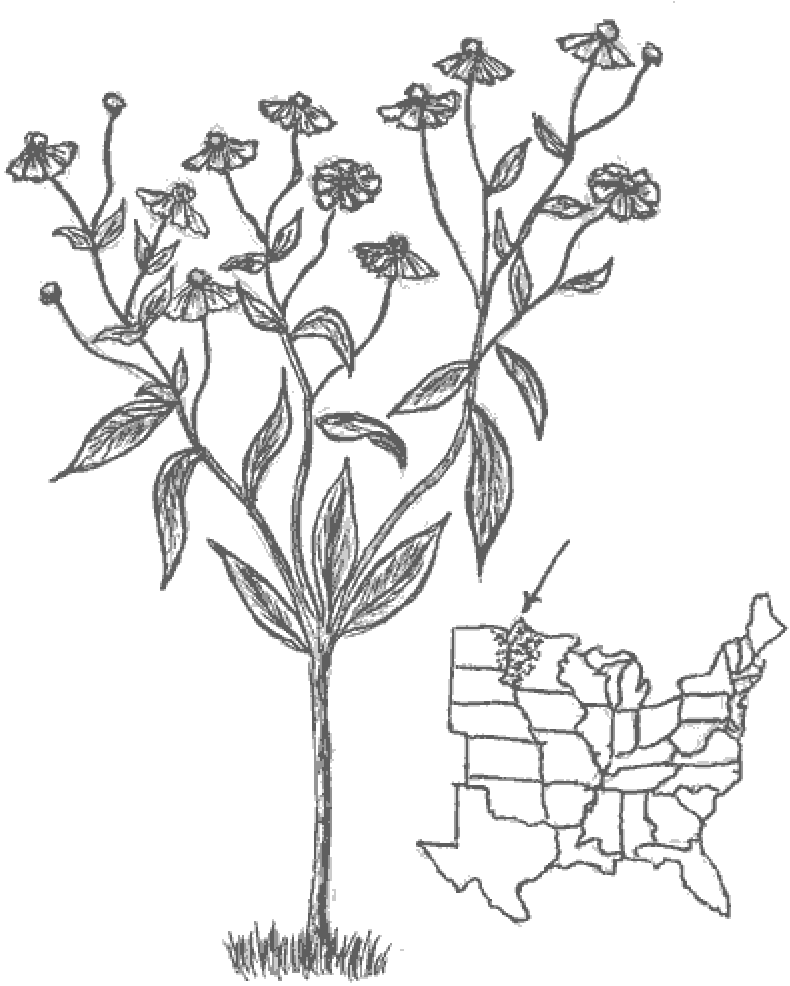
- Loose herding, avoiding dense areas of sneezeweed, results in less poisoning.
- Fence off or mow sneezeweed.
- Small patches may be eliminated by herbicides such as 2,4-D.

Comments

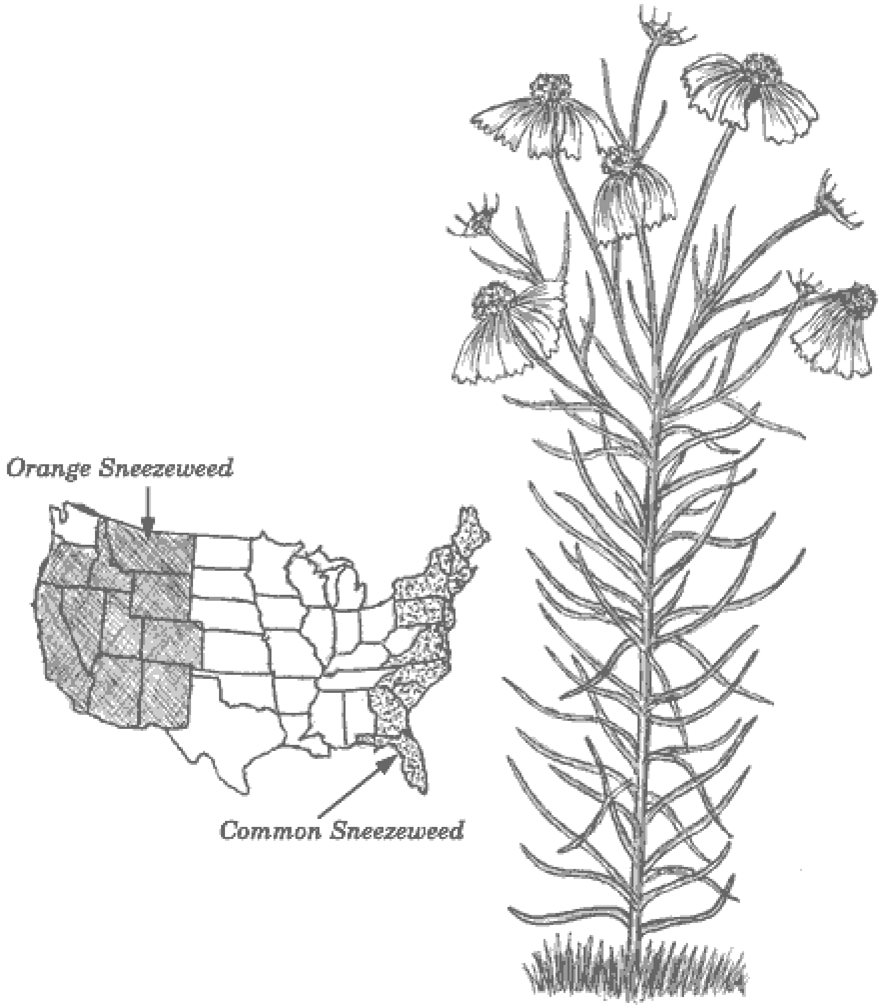
In the 1940s, it was estimated that 8,000 sheep were lethally poisoned by sneezeweeds annually.



Bitter Sneezeweed - *Helenium amarum* (Rafin), H. Rock. **- 1**, plant; **2**, flower head; **3**, seed. **Annual**, with short branching taproot. **Stems** smooth, erect, 6 to 30 inches (15 to 75 cm) tall, branching in upper portion. **Leaves** numerous, smooth, threadlike, without petioles, alternate, and crowded along main stem and branches. **Flower heads** about 3/4 inch (1.9 cm) in diameter, ray flowers yellow with toothed tip, surrounding dome-shaped mass of yellow disk flowers. **Seed** reddish-brown, hairy along edges, wedge-shaped, bearing bristle-tipped scales at top. **Found** in old feedlots, pastures, idle land, and wasteland. Does not persist under cultivation.



Common Sneezeweed, *Helenium Autumnale* L. - **1**, upper part of plant; **2**, lower stem and roots. **Perennial**, reproducing by seeds and a spreading crown. **Roots** much branched, somewhat fleshy, **Stems** slender, erect, smooth to rough, narrowly branched, with wide appendages along the stem, especially on upper part. **Leaves** alternate, slender, oblong to lanceolate, 2 to 4 inches (5 to 10 cm) long, gray and hairy when young, becoming greenish and smooth later. **Flower heads** sunflower-like, about 1 inch (2.5 cm) across. Ray flowers yellow, drooping, surrounding the greenish-yellow disk flowers. **Seed** about 1/16 inch (1.5 mm) long, hairy. **Found** around water holes and ditches where water is readily available. Whether dry or fresh, poisonous to livestock, especially sheep. Most serious in the Western areas.



Bitterweed plant in flower

Hymenoxys spp. - Rubberweed - Bitterweed

H. odorata - (*Actinea odorata*) bitter rubberweed, Colorado rubberweed, bitterweed
H. richardsoni (H. floribunda) - (*Actinea richardsoni*) pinque
H. lemmoni - Cockerell

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Poisonous Plants that Affect the Liver
Esp. sheep and goats, cattle, horses, swine, rabbits	Hours to chronic	Days to weeks; often lethal	

Family - Compositae (Composite or Sunflower Family)

Description

- *H. odorata*.
  - Plant - Annual, erect, bitter, small, bushy, up to 2 feet tall.
  - Stem - Usually purplish, thick, woody stalk, much branched from the base, base covered with a wooly growth, each ascending stem branches and terminates in a yellow-flowered head.
  - Leaves - Alternate to 3 times alternately divided into very narrow glandular, wooly divisions, not distinct from petiole.
  - Flowers - Composite flower heads at tips of stem branches, bright yellow, 1/5 - 1/2 inch in diameter. Sixty or more disc florets; 6 - 10 ray florets, rays tipped with 3 lobes; aster-like flowers, golden yellow or orange.
  - Fruit - 50 - 75 seeds from each head.

    - **Note** - Flowers in May or June. *H. richardsoni* is perennial.

Habitat

- *H. odorata* - Kansas to Mexico, and westward to California. Overgrazed ranges, along streams and low places.
- *H. richardsoni* - Saskatchewan to Texas, west to California and Oregon. Grassland, open forests, dry, sandy or gravelly soils.

Toxic Principle

The water soluble toxic principle is believed to be the sesquiterpene lactone hymenoxon, although other compounds including hymenolide, parcin and psilostrophin also present. Hymenorin is an epimeric mixture of hymenoxon.

Susceptible Species

Sheep are more susceptible than cattle and goats. Natural cases largely limited to sheep, and no notable reports of toxicosis in cattle, horses and goats. Sheep may develop a liking for it.

Toxicity

- General.
    - Toxicity is retained upon drying.
    - Wide variation in minimum lethal dose.
    - Bitterweed toxicity slowly increases with maturity.
    - Toxicity is greatly increased during drought.
    - Ingestion of 1.3% of body weight may be lethal to some animals during periods of normal rainfall and 0.5% may be lethal during drought.
    - Bitter taste, therefore, often avoided by range livestock.
    - An animal may die from eating one large feeding, or repeated smaller feedings over extended periods of time.
    - Winter and spring seems to be the most dangerous time.
- Sheep.
    - One percent of animal's weight as green plant is lethal, whether ingested at one time or in fractional amounts over several months.
    - A 100-lb animal may die if it eats 0.25 - 0.5 lb daily for 2 - 4 weeks.
    - Hymenovin is lethal to sheep when given orally at doses as low as 100 mg/kg.

Mechanisms of Action

- Binds to sulfhydryl groups (like arsenic and certain other metals) and other nucleophilic components.
- Mixed function oxidase inducers and inhibitors had no effect on toxicity of hymenoxon.
- Cysteine or methionine, a source of SH groups, or BHA (butylated hydroxyanisole), which increases glutathione and GSH transferase, reduced the toxicity of hymenoxon.

Signs

- Loss of appetite, anorexia, apparent abdominal pain.
- Cessation of rumination, bloating.
- Vomition, salivation.
- Green salivary discharge and stains about the muzzle, commonly seen in range cases.
- Affected sheep commonly lag behind the rest of the flock.
- Death may occur in 1 - 3 days.

Lesions

- Kidney, liver, lungs and abomasum may be congested.
- Liver may be friable.
- Abomasum and duodenum contain hemorrhages.

- Submaxillary and retropharyngeal lymph nodes are frequently congested or hemorrhagic.
- Spleen may be enlarged.
- Epicardium, endocardium and costal pleura may be hemorrhagic.
- Few if any lesions may be found in some chronic cases.

Diagnosis

- Identification of the plant.
- Evidence of consumption.
- Appropriate clinical signs and lesions.

Treatment

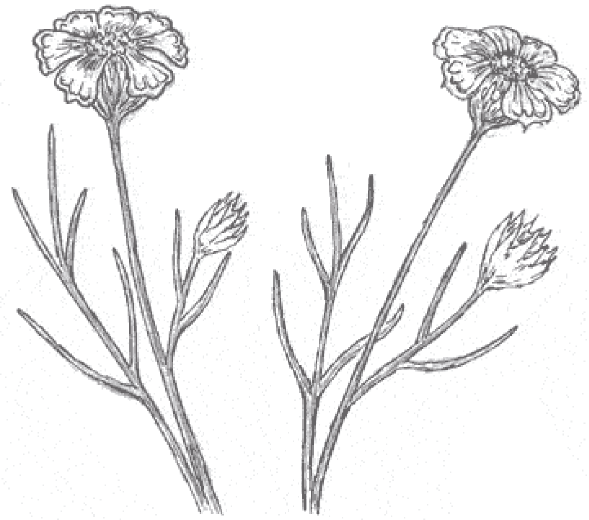
- If removed from access to the plant at the onset of signs, sheep may make an uneventful but slow recovery.
- See *Helenium*.

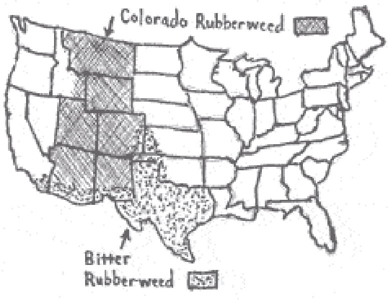
Prevention

- Reduce stocking rates.
- Since animals will seldom eat toxic amounts, heavy losses may be prevented, especially when sheep are being driven, by avoiding heavily infested areas or by supplemental feeding.
- When sheep losses become especially high, cattle should be grazed on the affected pasture in their place.
- Eradication of the plant is usually not practical. Efforts may include pulling by hand or the use of 2,4-D.

Comments

- Edward's plateau reports the most losses (in Texas).
- The name rubberweed is used because the plant contains a small amount of rubber.





Kochia Scoparia

Kochia scoparia - Kochia, Mexican fireweed, fireweed, summer cypress, burning bush

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Ruminants	Hours to chronic	Days to weeks; potentially lethal	

Description

- An annual plant reproducing by means of seeds.
- Stems - Smooth, green, much branched, from a few inches to over 6 feet in height.
- Leaves - Alternate, simple, hairy, 1 - 2 inches (2.5 - 5 cm) long, pointed, without petioles.
- Flowers - Small, greenish, without petals, in axils of upper leaves and in terminal panicles.
- Seeds - About 1/16 inch (1.5 mm) long, oval, flattened with groove on each side, finely granular, surface dull brown with yellow markings. Fragile star-shaped hull may enclose seed.
- Root - Taproot.

Habitat

- *Kochia scoparia* is extensively used as a forage plant for cattle in arid, infertile regions of the western and southwestern United States. Problems are sometimes encountered in areas of Colorado, New Mexico, and Texas.
- *Kochia* tolerates extremely high soil sodium concentrations and in areas of such soil may exist as virtually the only species present.

Toxic Principles

- Some *Kochia scoparia* plants contain a substance (which may or may not actually be a thiaminase) which destroys thiamine. This agent does not apparently account for the principle effects of *Kochia* toxicosis.
- May contain oxalates (at up to 6 - 7% of the dry weight), but usually no oxalate crystals are observed in the kidneys of *Kochia* poisoned animals.
- May contain nitrates (see section on nitrate toxicosis).
- May also contain "saponins and/or alkaloids".
- May also contain other, but as yet, unidentified hepatotoxic and nephrotoxic and possible neurotoxic substances.
- Often contains high sulfate concentrations.

Toxicity

- In the southwest USA, *Kochia* grows wild and is sometimes touted as a good forage plant. It is high in crude protein and may be fed to cattle and horses.
- Problems principally arise from mid-summer onward. Most poisoned animals are first clinically affected from mid-August to the first of September after grazing for 35 - 40 days.
- Drought seems to increase the likelihood of *Kochia*-related problems. Whether this is due to a reduction in the availability of other plants or increased concentration of the toxic chemicals in *Kochia* is not known.
- Seed maturation also seems to increase toxicity of the plant.

Mechanisms of Action

- Laxative effect is believed to be due to the high sulfate content of *Kochia*.
- Most common major toxic effect is due to hepatotoxicity.
- Photosensitization, which is not rare, is likely to be due to hepatotoxicity.
- Central nervous system derangement may be due to polioencephalomalacia secondary to thiamine deficiency as a result of *Kochia*-induced thiamine destruction.
- Nitrate toxicosis induces its effect as a result of gastrointestinal microbial conversion of nitrate to nitrite which oxidizes hemoglobin to methemoglobin which no longer carries oxygen.

- Soluble oxalates may be nephrotoxic and precipitate as calcium oxalate in the kidney or may cause acute hypocalcemia, also due to combination with available calcium.

Signs and Clinical Pathology

- Signs will vary depending upon which *Kochia*-induced toxic effect, if any, predominates.
- *Kochia scoparia* produces loose feces whenever it is grazed.
- Liver failure may be evidenced by an increase in liver-associated enzymes in the serum prior to the onset of clinical signs in addition to subsequent profound icterus. Bilirubin may also be quite high and elevations in pyruvate, lactic acid, and creatine kinase have also been observed. Signs referable to liver failure may also include lagging behind the rest of the herd, anorexia, evidence of abdominal pain, bilirubinuria, and death.
- Photosensitization may occur and be accompanied by icterus. Photosensitized animals display lesions similar to severe sunburn on the white (unpigmented) areas of the body.
- Blood urea nitrogen values may also increase.
- Animals with polioencephalomalacia (cerebrocortical necrosis) from any cause may display bizarre behavior, a severe drop in responsiveness to external stimuli, blindness, muscle tremors especially of the head, cerebral edema, and terminally, opisthotonus, nystagmus, and clonic-tonic convulsions.

Lesions

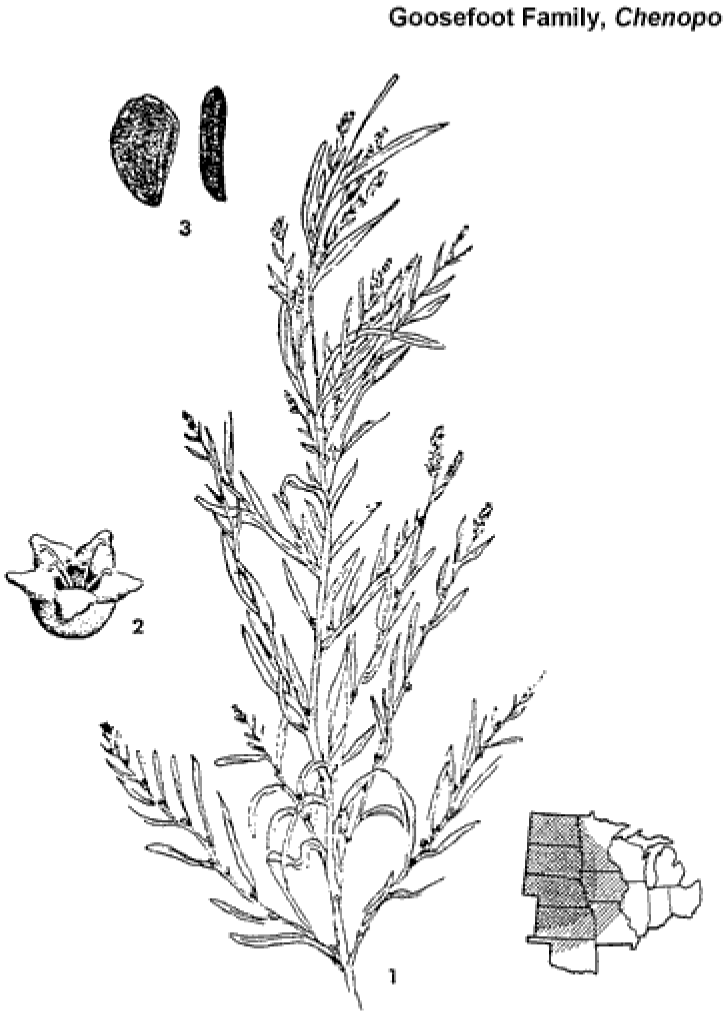
- Also vary depending upon the clinical syndrome present.
- Severe liver necrosis is the most common lesion, and hepatic cirrhosis may be seen.
- Lesions compatible with photosensitization or polioencephalomalacia (both of which are thoroughly described in other references) may be seen in some animals experiencing *Kochia* poisoning.
- Gastrointestinal tract inflammation may be seen.

Diagnosis

- Appropriate clinical signs and lesions and sufficient consumption of *Kochia* in addition to evidence of ruling out other causes.
- Criteria for the diagnosis of polioencephalomalacia are readily available in other references.
- See also Bracken Fern (*Pteridium*) under Diagnosis.

Treatment

- Terminate exposure to **Kochia**.
- There is no specific treatment for **Kochia**-induced hepatotoxicosis. Minimization of stress is appropriate. Manage as for other causes of liver failure.
- If possible, animals with photosensitization should be kept out of the sunlight by confinement indoors.
- Treat polioencephalomalacia cases with thiamine.
- Nitrate poisoning and oxalate toxicosis are discussed in separate handouts in this series.



Kochia, *Kochia scoparia* (L.) Schrad - **1**, entire plant; **2**, individual flower; **3**, seeds. **Annual**, reproducing from seeds. **Stems** smooth, green, much branched, from a few inches to over 6 feet (1.8 m) high, growing from a taproot. **Leaves** alternate, simple, hairy, 1 to 2 inches (2.5 to 5 cm) long, pointed, without petioles. **Flowers** small, greenish, without petals, in axils of upper leaves and in terminal panicles. Seeds about 1/16 inch (1.5 mm) long, oval, flattened with groove on each side, finely granular, surface dull, brown with yellow markings. Fragile star-shaped hull may enclose seed. **Found** in cropland, dry pastures, and rangeland, where it is a serious weed. Also commonly known as Mexican fireweed.

Lotus Corniculatus - Birdsfoot Trefoil

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Poisonous Plants that Affect the Liver
Ruminants; other herbivores	Chronic	Weeks to months; poisoning is rare	

Family - Leguminosae (Pulse or Bean Family)

Habitat

- Europe, Britain, Australia, Africa, and the USA.
- A forage crop (used in the midwestern USA and elsewhere).

Clinical Signs and Lesions

- Losses reported primarily in Australia.
- A cyanogenic substance is reportedly present in some strains, and cyanide toxicosis in various horses and mules was reported in Russia.
- Liver failure occasionally has been associated with trefoil pastures, apparently due to a different toxic principle.
- Dermatitis has been associated with exposure of several species of animals to this plant.

- This may be related to primary (or perhaps secondary) photosensitization.

- Potentially associated with bloat in cattle due to saponins.
- Grazing trefoil may slow the growth rate of young chickens.

Diagnosis

Toxicosis may be difficult to confirm and other possible causes must be ruled out.

Birdsfoot Trefoil, (*Lotus corniculatus* L.)

Family - Pea (Leguminosae).
Growth Form - Perennial herb from elongated roots.
Stems - Spreading to ascending, smooth or slightly hairy, up to 18 inches long.
Leaves - Alternate, divided into 5 leaflets, the leaflets oblong to obovate, rounded or pointed at the tip, up to 1/2 inch long, smooth or nearly so, up to 2/3 inch long.
Flower Arrangement - Flowers several, borne in umbels, the umbel borne on stalks.
Flowers - Bright yellow, up to 3/4 inch long, borne on short stalks.
Sepals - 5, green, united below.
Petals - 5, bright yellow, arranged to form a typical pea-shaped flower.
Stamens - 10.
Pistils - Ovary superior.
Fruits - Pods narrow, up to 1 inch long, pointed at the tip, with several seeds.
Habitat - Open, disturbed areas.
Range - Throughout the state.
Time of Flowering - June to September.

Cycad Poisoning

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Poisonous Plants that Affect the Liver
Herbivores, dogs, swine	Hours to a few days	Weeks to permanent damage; often lethal	

Description

- Cycad palms occur in tropical and subtropical climates.
- Representative genera and their geographical locations include *Encephalartos* spp. (Africa), *Diion* spp., and *Zamia* spp. (Central America), *Cycas* spp. (Oceania, Australia), *Lepidozamia* spp., *Bowenia* spp., and *Macrozamin* spp. (all 3 in Australia).
- Cycads (*Zamia* spp.) are native to Florida, and many non-native species have been cultivated as ornamentals. Cycads (*Cycas revoluta*, common name: false sago palm) has also been a cause of toxicosis in dogs in Texas where it is grown as an ornamental.
- *Zamia floridana* - common name Coontie - fernlike plant with a thick starchy stem. Leaves (0.3 - 1 cm long) are feather-shaped. Slender cylindrical (7.6 - 18 cm) cones on male plants with thicker (13 - 18 cm) cones present on female plants.

Poisonous Principles

- Glucoside derivatives of methyl azoxymethanol (azoglycosides) including cycasin, macrozamin, and alpha-amino-beta-methyl-aminoproprionic acid.
- Cycasin has been demonstrated to be responsible for acute hepatotoxic and carcinogenic effects following ingestion of cycads. However, cycasin is not responsible for neurotoxicity in livestock.
- Cycasin is not carcinogenic when administered parenterally. Cycasin must be hydrolyzed to its aglycone, methylazomethanol to induce tumors.
- Some evidence of additional neurotoxic compounds having a molecular weight of 1,000.
- Pois-Index ® has listed cycads as containing cyanogenic glycosides. However, the authors are aware of no evidence for the presence of cyanogenic glycosides, and the clinical syndromes are not consistent with a cyanogenic compound ingestion.

Toxicity

- As few as 2 seeds of a cycad plant have caused poisonings in small dogs.
- Cycad-based meals are occasionally incorporated as a staple of the diet of some people.

Susceptible Species

- Cattle, sheep, dogs, swine, horses, goats.
- Humans.

Clinical Syndromes

- Acute intoxication characterized by hepatic (ascites, icterus) and gastrointestinal signs (vomiting, anorexia). Clinical signs develop within 12 hours of ingestion.
  - Polydipsia.
  - Hepatic cirrhosis. Icterus develops within 2 - 3 days postingestion.
  - Hemorrhagic gastroenteritis with gastric or abomasal ulceration.
  - Coagulopathy, subcutaneous bruising, and hemorrhage. Melena and hemoptysis occur terminally.
    - Thrombocytopenia. Prolonged PT, ACT, PTT.
    - May be due to hemorrhage, decreased synthesis of clotting factors, and/or DIC.
- Cattle, sheep.
  - Neurotoxic syndrome.

    - Cattle - "goose-stepping" gait, ataxia more severe when animals are exercised. Condition in cattle known as "derriergue" in Dominican Republic.
    - Goat, sheep - progressive hindlimb paralysis.
- Cardiotoxic effects reported.
- Cycasin potentially carcinogenic in laboratory animals.
- Associated with high incidence of amyotrophic lateral sclerosis and Parkinsonism - dementia in humans (Guam).

Clinical Pathology

- Hyperbilirubinemia, hypoproteinemia, hypocalcemia, hyponatremia, hypokalemia, azotemia, and a metabolic alkalosis may occur.
- Increased serum liver enzymes (may not be pronounced).
- Glycosuria, bilirubinuria, hematuria, and casts on urinalysis.

Lesions

- Centrilobular and midzonal hepatic necrosis. Distended bile ducts. Generalized icterus, petechial, and ecchymotic hemorrhage, and ascites may be present.
- Desquamation of renal tubular epithelial cells. Proteinaceous, red blood cell, and bilirubin casts may be present.
- Degeneration of fascilus gracilis and lateral spinocerebellar pathways. Axonal degeneration.

Treatment

- Symptomatic and supportive.
- Prognosis for cycad poisoned dogs is generally poor.

Hepatogenous Photosensitizers

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Tetradymia - Artemisia Poisoning

T. glabrata - Littleleaf
T. canescens - Horsebrush, coal oil brush, spring rabbitbrush
T. axillaris
A. nova - Black sagebrush

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Hepatogenous Photosensitizers
Sheep	Hours to days	Days to weeks, potentially lethal	

Family (both genera) - Compositae (Composite or Sunflower Family)

Description (*Tetradymia*)

- Plant - low spreading, strongly scented shrub; 1 - 3 feet high.
- Stem - woody, densely branched. Young branches pale green, older ones gray; early on they are covered with white wooly hairs.
- Leaves - alternate, entire, small, fleshy or may end in spines. Linear, sharp-pointed, less than 1/2 inch long; secondary leaves in clusters.
- Flowers - yellow, maturing to gray. Disk flowers with yellow corolla. Inflorescence is a composite head with peduncles about the periphery of the plant. Each head is composed of 4 yellow florets.
- Fruit - achenes, 5-nerved, capillary, bristly.

Habitat

- Rocky Mountain states. Hills of arid areas, deserts, well-drained sites.
    - *T. canescens* - sagebrush areas and foothills.
    - *T. glabrata* - one of first plants to become green in spring.

Toxic Principle

- *Tetradymia*
    - Hepatotoxin.
    - Cumulative resin.
    - Furanoeremophilanes (furanosesquiterpenes), especially tetradymol is metabolized by mixed function oxidases to a more toxic substance. Furanoeremophilanes uncouple oxidative phosphorylation in electron transport.
    - Phylloerythrin from other plants must be eaten to result in the development of photosensitization.
- *Artemisia*

    When consumed at about the same time as *Tetradymia*, the highly pigmented *Artemisia nova* (black sagebrush), which generally contains sesquiterpene lactones, often sets the stage for *Tetradymia*-associated photosensitization.

Susceptible Species

- Sheep.
- Note cattle and horses reportedly won't eat *Tetradymia*.

Toxicity

- General
    - *T. glabrata* is about 2.5 times more toxic than *T. canescens*.
    - Toxicity is greatest in April to late July.
- Sheep
    - 2 lb per head per day for 2 days (of young *Tetradymia* buds) is a fatal dose.
    - Approximately 1/2 lb of leaves of little leaf horsebrush or 1 1/4 lb of spineless horsebrush will usually cause bighead in a 100-lb sheep.

Signs

- Sheep
    - Acute signs may develop within a few hours.
    - Weakness, collapse, death after coma or convulsions.
    - Subacute signs develop in 1 - 3 days.
    - "Bighead" - itching, uneasiness, swelling of head, inflammation of eyes, blindness, serum oozes from scabs, etc.
    - Abortion and sterility may occur.

Clinical Pathology and Lesions

- Degenerative changes in liver and kidney.
- Serum enzymes elevated.
- Icterus is not typical.

Diagnosis

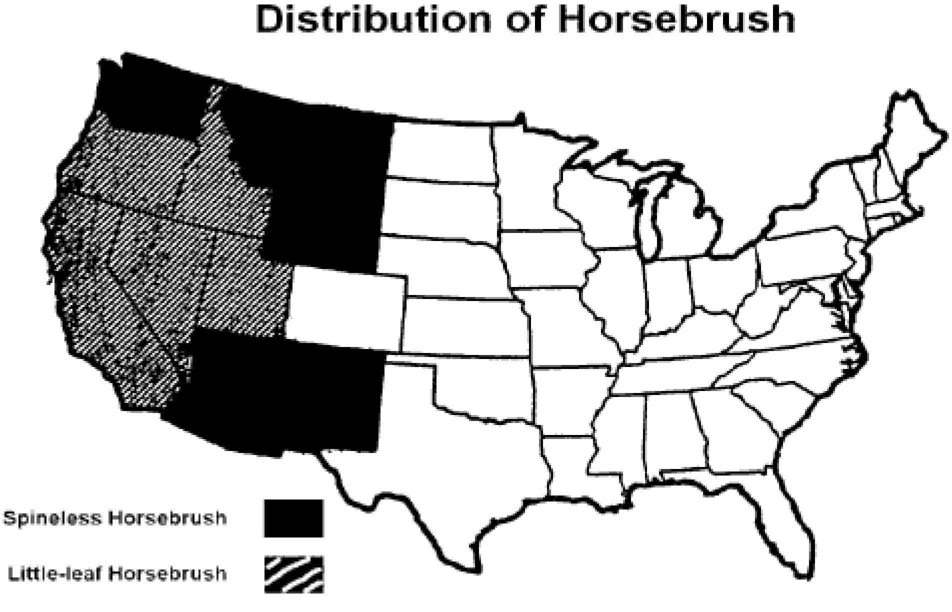
Identification of *Tetradymia*, evidence of consumption, appropriate signs and lesions.

Prevention

Sheep will selectively avoid *Tetradymia* unless nothing else is available. May consume the plant if pushed along the trail too rapidly.

Comments

T. glabrata appears in the early spring when other forage is unavailable and poisoning occurs largely at that time, however, poisoning occasionally occurs in the fall as well.



***Panicum* spp. - Panic Grasses**

P. antidotale - Blue panicum
P. coloratum - Kleingrass 75
P. dichotoflorum
P. schinzii
P. virgatum

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatogenous Photosensitizers
Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal	

Descriptions

- *P. antidotale*
    - Plant - perennial, warm-seasoned bunchgrass, grows in large dense tufts, bluish-green, drought resistant, 4 feet tall.
    - Stem - branches freely at nodes; when mature is woody and coarse.
    - Rootstock - short, bulbous rhizomes.

Habitat

New Zealand, Australia, South Africa, South America, Afghanistan, India, South Texas plains, high plains, Edward's Plateau, and Trans-Pecos area of Texas. Kleingrass is a warm-season bunchgrass, introduced from Africa, and is established on at least 500,000 acres in Texas.

Poisonous Principles

- Lithogenic (stone-forming) steroidal saponins are responsible for formation of crystals in the bile ducts.
- **Note**: Saponins = a sapinogenin + a sugar moiety. The sapinogenin in *Panicum* is believed to be a diosgenin, that is the same as, or similar to those, of several poisonous plants that also cause photosensitization and crystals in the bile ducts, including *Tribulus, Nolina,* and *Agave*.

Mechanism of Action

- The sapinogens reportedly crystallize out in bile ducts resulting in hepatogenous photosensitization.
- At this time it seems likely that another compound in addition to the sapinogen is needed for photosensitization to develop.

Susceptible Species (see also Toxicity)

Sheep, cattle. Note: Cattle do well on Kleingrass 75, but it tends to be toxic to sheep.

Toxicity

- Sheep.
    - In Kleingrass toxicosis (of lambs), age is a factor; adults are more resistant.
    - Thirty to 50% losses of flocks of sheep on irrigated blue panicum following heavy application of nitrogen fertilizer have been documented.
    - Twenty-one of 40 lambs were affected by Kleingrass toxicosis after grazing for 5 - 8 days.
    - In 2 other outbreaks, 25 and 60% of the lambs on the pasture were affected.
    - Kleingrass with flowers or seeds is apparently more toxic.
- Cattle.
    - Cattle on Kleingrass were unaffected on pastures which were subsequently associated with severe illness and death after photosensitization in lambs.
    - Severe losses of cattle may occur, however, from grazing irrigated, fertilized blue panicum.

Signs

- Sudden illness.
- Possibly hepatogenous photosensitization.
- Rapid breathing.
- Death may occur within a few minutes of the first clinical signs.
- Swollen heads, necrosis of the skin of the ears, mild icterus and lassitude.

Lesions

- Hepatocellular damage is likely to be found on histopathology.
- In Kleingrass toxicosis, there were enlarged and vacuolated hepatocytes, mild degenerative changes in the renal tubules and a degenerative focal myocarditis concentrated at the base of the papillary muscles.
- Birefringent crystals may be evident in the bile ducts, skin, kidney, adrenal gland, and heart. Frozen sections are necessary since processing for paraffin embedding is likely to dissolve the crystals.
- Horses experimentally exposed to Kleingrass pastures or given Kleingrass hay had increased amounts of collagen in hepatic sinusoids.
- Pulmonary edema and emphysema occurred in blue *Panicum* toxicosis.
- In lambs, the thoracic cavity may be partially filled with straw-colored fluid containing fibrin.
- Blood is dark, almost black suggesting antemortem anoxia.

Diagnosis

Identification of *Panicum*, evidence of consumption, appropriate clinical signs and lesions.

Treatment

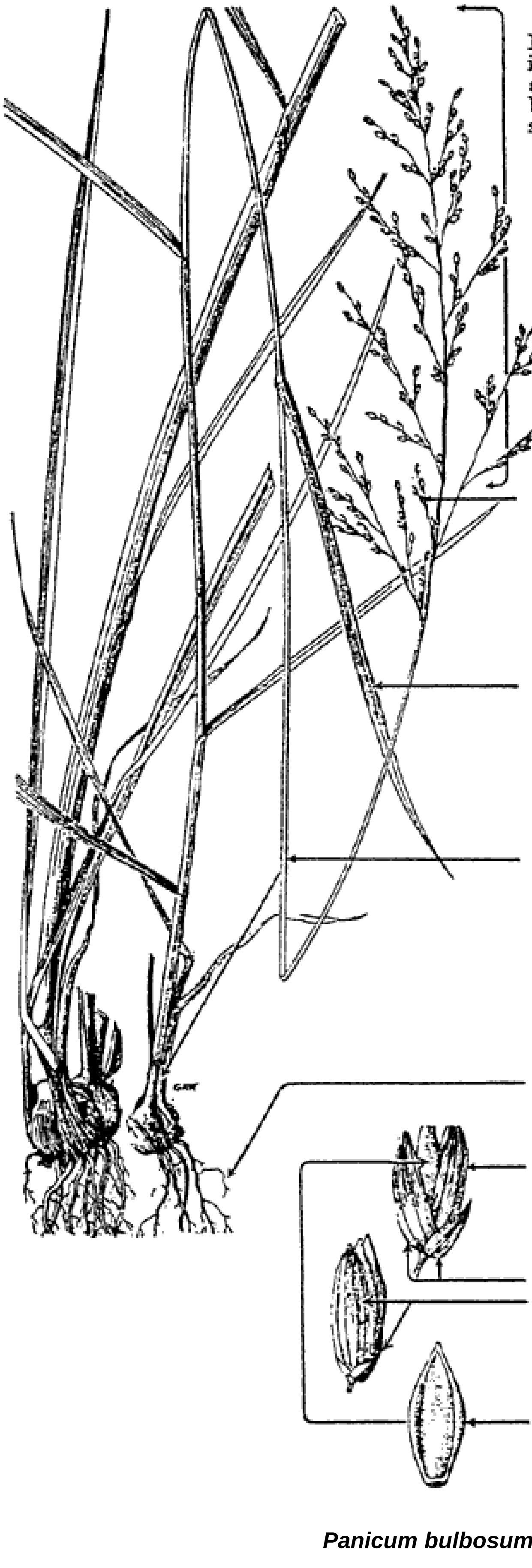
Nursing care, good nutrition and shelter (shade) to reduce exposure to sun is appropriate.

Prevention

Cattle and sheep should not be allowed to graze blue *Panicum* for at least 40 days after fertilization and irrigation should be closely regulated.

Comments

- Blue *Panicum* is a valuable forage crop, when properly managed for grazing and hay.
- Rotational grazing in small blocks is necessary to obtain good utilization during peak production periods.
- The coarse unpalatable stems that are not grazed should be mowed to force nutritious basal growth for the next rotational grazing period.



Flower head (panicle)—open, 8 to 25 in. long, with single or clustered, wavy, ascending or somewhat spreading branches, long-exserted from top leaf sheath

Individual flower groups (spikelets)—commonly purplish, about ⅛ in. long, hairless, somewhat pointed at tip, 2-flowered; lower flower imperfect; upper flower perfect

Leaves—8 to 24 in. long and ¼ to nearly ½ in. wide, flat, erect or ascending, somewhat harsh, especially on upper surface, often hairy near base

Stalks (culms)—tufted, erect, 3 to 7 ft. high, stout, smooth, with hard, bulblike enlargements ("corms") at base

Roots—fibrous, strong

Imperfect flower—reduced to a 5-nerved bract (sterile lemma) which rarely encloses a male flower

Lowest (2) spikelet bracts (glumes)—very unequal, both falling with "seed"; 1st, usually 3-nerved, about ½ as long as 5-nerved 2d glume

Outer flower bract (lemma)—about as long as spikelet, soon folded around "seed", transversely wrinkled

Panicum bulbosum - Panic grass

Tribulus - Puncture Vine

Tribulus terrestris - Puncture vine, caltrop, goathead

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatogenous Photosensitizers
Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal	

Family - Zygophyllaceae

Habitat

- Colorado west to California and south to Mexico, Pacific Northwest.
- Less common in the Atlantic States.
- Waste places, along trails, roadsides, overgrazed pastures.

Description

- Plant - a prostrate annual weed.
- Stem - Prostrate or trailing, branched, up to 3 feet in length from the base.
- Leaves - opposite, pinnate, compound; leaflets - 4 - 7 pairs; oblong to elliptical, 1/2 inch long.
- Flowers - single, small axial, short-peduncled; 4 or 5 pale, yellow petals; 4 or 5 sepals; pistil of 5 carpels; 2 - 4 spreading prickles, 10 stamens.
- Fruit - small, bony capsule, 5 nutlets with strong spikes, one or few seeded at maturity; flattened.
- Rootstock - taproot.

Poisonous Principles and Mechanism of Action

- See Poisonous Principles and Mechanism of Action section in the *Panicum* section of these notes. It has been suggested that *Panicum*, *Tribulus*, *Nolina*, and *Agave* all have poisonous principles and toxic effects similar to those of *Panicum*.
- May also contain dangerous concentrations of nitrate.

Toxicity

- Spiny burs cause mechanical damage.
- Toxin in leaves of preflowering to fruiting plants.
- High mortality among young animals.

Susceptible Species

Sheep.

Clinical Signs

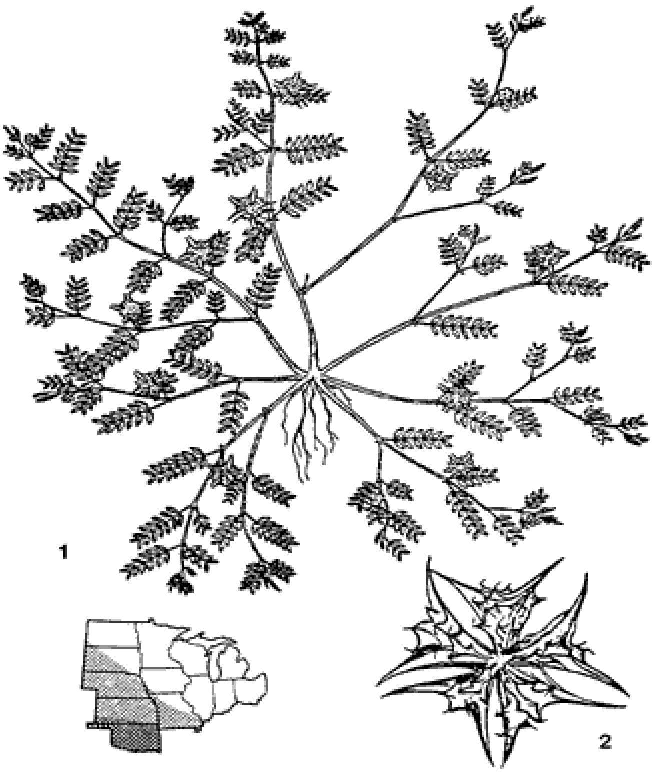
Bighead, swelling of ears and head and other signs reflecting photosensitivity.

Lesions

- Intensely yellow fat throughout body.
- Lesions of the skin reflecting photosensitivity.
- Crystals may be noted in the bile ducts.

Diagnosis

Identification of *Tribulus*, evidence of consumption, appropriate clinical signs and lesions.



Puncturevine *Tribulus terrestris* - L. **1**, plant; **2**, seed pod showing burs. **Annual**, reproducing by seeds. **Root system** simple taproot. **Stems** hairy, prostrate, branching from base to form dense mats of slender trailing branches 6 to 8 feet (1.8 to 2.4 m) long. **Leaves** oblong, opposite, hairy, divided into pinnate leaflets. **Flowers** small, yellow, 5-petaled, produced in axils of leaves. **Seed pods** contain 5 burs, each having 2 sharp, long, stout, rough spines, strong enough to penetrate shoe soles or bicycle tires. **Burs** separate as they mature and often lie in the soil for years before germinating. **Found** in pastures, roadsides, and waste places, along railroad tracks, and sometimes in cultivated fields. A serious weed, listed as noxious in some states. Cattle do not graze areas infested with puncturevine.

Nolina

Nolina texana - Bunchgrass, Sacahuiste
N. microcarpa

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatogenous Photosensitizers
Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal	

Family - Liliaceae (Lily Family)

Description

- *N. texana*.
  - Plant - perennial, grows in clumps, 6 inches tall, 1 foot in diameter.
  - Stem - short; woody, enlarged at base, most buried, much branched; branches stubby; stem and branches form a trunk-like structure.
  - Leaves - cluster of basal, linear, leaves, finely serrate margins, numerous, 1/4 inch broad to 5 feet long; prominent ridge in concave upper surface; distinctly triangular in section near tip.
  - Flowers - several flowering stems, erect; numerous, flowers, white, long-lived, small, 6-parted, in a large panicle with persistent white perianth of 6 parts.
  - Fruit - 3-valved capsule with few seeds; mostly separate carpels.

Poisonous Principles and Mechanism of Action

- See Poisonous Principles and Mechanism of Action section in the *Panicum* section of these notes. It has been suggested that *Panicum, Tribulus, Nolina*, and *Agave* all have poisonous principles and toxic effects similar to those of *Panicum.*
- May also contain dangerous concentrations of nitrate.

Susceptible Species

Cattle, sheep, goats.

Toxicity

- General.
    - Retains toxicity upon drying.
    - Flowers and fruit are toxic to livestock.
    - Foliage appears to be non-toxic.
    - Minimum toxic dose and minimum lethal dose are almost the same.
    - Most poisonings occur in early spring when plants are blooming.
    - Heavy blooms occur once every 5 or 6 years.
    - Severe outbreaks of poisoning may occur during years of heavy blooms.
- Sheep.
    - Minimum toxic dose is approximately 1.1% of animal's body weight of buds or blooms.

Signs and Lesions

- Anorexia, lassitude.
- Icterus occurs in 1 or 2 days.
- Yellow or red urine most likely due to hemoglobinuria.
- Yellow nasal and ocular discharges.
- Progressive debilitation, death within 1 week of onset of symptoms.
- Crystals may be present in the bile ducts.
- Photosensitization may occur (swollen face and ears).
- Dermatitis with itching may occur in early stages of photosensitization.
- A purplish band may appear around the top of the hoof above the coronary band.

Lesions

- Generalized jaundice.
- Yellow-brown liver and greenish black swollen kidneys.
- Centrilobular degeneration of liver.
- Fatty and albuminous degeneration of liver and kidney.
- Kidneys swollen.

Diagnosis

Identification of *Nolina* and evidence of consumption and appropriate clinical signs and lesions.

Treatment

- Shade and nutritious feed, remove from access to plant.
- Most animals developing severe jaundice will die.

Prevention

Remove animals from sacahuiste-infested pastures during the time the plant is in bloom and early fruit.

Comments

When grasses are dry, sacahuiste leaves are green; they are browsed and some nutrition is obtained.

Agave Lecheguilla - Agave

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatogenous Photosensitizers
Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal	

Family - Amaryllidaceae (Amaryllis family)

Description

- *A. lecheguilla*
  - Leaves - 1 - 1 1/2 inches wide, 12 - 24 inches long, ascending with recurving prickles, terminate in a sharp spine; basal, thick, spiny 4-12 inches long.
  - Flowers - narrow, yellow, elongated clusters with 2-6 flowers per cluster. Each flower is 1 1/2 - 2 inches long. After 10 - 15 years of vegetative growth, the plant flowers once, producing a large, spikelike panicle on a thick stalk 6 - 12 feet tall and then dies. New plants may be formed from the seeds and also from the offsets from the parent plant. Flowers are tubular with 3 sepals, 3 petals, 6 stamens, and a 3 carpellate pistil which matures into a leathery capsule containing many black, flattened seeds in its 3 cavities.

Habitat

Texas and New Mexico to Mexico; Trans-Pecos area of Texas. Dry hills, elevated valleys, edges of canyons, low limestone hills, dry valleys, low rainfall areas along the Rio Grande. Several species are cultivated and used for the production of alcoholic beverages (mescal, tequila). Fiber of the leaves is used to make rope or twine.

Poisonous Principles and Mechanism of Action

- Contains a diosgenin that results in crystal formation in bile ducts. See Poisonous Principles and Mechanism of Action section in the *Panicum* section of these notes. It has been suggested that *Panicum, Tribulus, Nolina*, and *Agave* all have poisonous principles and toxic effects similar to those of *Panicum.*
- *Agave* also has a separate photodynamic agent, which is independent of liver and kidney damage.
- May also contain dangerous concentrations of nitrate.

Susceptible Species

Sheep, goats, humans, cattle, rarely horses.

Toxicity

- The sap, thorns, and other parts are toxic.
- Liver damage is of primary significance in toxicosis, photosensitivity is of secondary importance.
- The photodynamic agent is toxic to animals exposed to direct sunlight after feeding on the plant.
- The hepato-renal toxin is not activated by the light.
- Consumption of as little as 1% of an animal's body weight may produce serious toxicosis and death.
- One-half to 1 lb daily fed to sheep or goats produces photosensitization in less than a week and death due to liver and kidney damage in 1 - 2 weeks.
- A puncture wound from an *Agave* plant in a human was reported to cause shock.
- Animals are most commonly poisoned during the winter and spring, especially in drought years when other forage is scarce.
- Morbidity may reach 30% along with some mortality.

Signs

- Contact dermatitis on contact with the plant, especially the sap.
- Listlessness, lag behind the flock or herd.

- Progressive decrease in water and feed consumption.
- Progressive weakness and emaciation.
- Icterus.
- Photosensitization.
- Edema of face and ears; "swell-head", "goat-fever".
- Yellow discharge about the eyes and nostrils.
- Purplish zone beneath the coronary band of the hoof.
- Urine is dark (port wine) colored.
- Plant may cause laxative or irritant effect, especially when eaten in quantity.
- Coma of short duration may precede death.

Clinical Pathology

- Pronounced icterus.
- Albuminuria.

Lesions

- Acute toxic hepatitis and nephritis.
- Liver may be light brownish-yellow, capsule thickened.
- Crystals may be present in the bile ducts.
- Kidneys may be swollen and greenish-black; numerous pinpoint gray specks.
- Gallbladder may be distended but bile usually appears normal.
- Decreased erythrocyte count in some cases.
- Polymorphonuclear leukocytes may comprise 90% of the leucocyte count.

Diagnosis

- Identification of *Agave lecheguilla*, evidence of consumption, appropriate clinical signs and lesions.

Treatment

- Shade to minimize exposure to the sun (applies to all cases and types of photosensitization).
- Nutritious diet.

Prevention

- Supplement feed when the animals are exposed to the plant and are inclined to consume it.
- Reducing the stocking rates of the range.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Hepatogenous Photosensitizers
Blue-green algae (*microcystis*)	(See Poisonous Plants that Affect the Liver)			
Rape (*Brassica*)	(See Goitrogenic Plants)			
Kochia Scoparia	(See Poisonous Plants that Affect the Liver)			
Moldy post-frost Florida Bermuda Grass (Cynodon)	Herbivores	Days to weeks	Weeks to months	
Pyrrolizidine alkaloids plants	(See Poisonous Plants that Affect the Liver)			
Lantana	(See Poisonous Plants that Affect the Liver)			

Sporodesmin (mycotoxin)	(See Mycotoxins that Affect the Liver)	

- *Sporodesmin (Mycotoxin) (See Mycotoxins that Affect the Liver)
- Pyrrolizidine Alkaloid Plants (See Poisonous Plants that Affect the Liver)
- Lantana (*Lantana*) (See Poisonous Plants that Affect the Liver)
- Moldy post-frost Florida Bermuda Grass (*Cynodon*)
- Blue-green Algae (*Microcystis* spp.) (See Poisonous Plants that Affect the Liver)
- Rape (*Brassica*) (See Goitrogenic Plants)
- Kochia (*Kochia scoparia*) (See Poisonous Plants that Affect the Liver)
- Alsike Clover (*Trifolium hybridum*) (See Estrogenic Toxicants)
- Congenital Liver Anomale - Southdown sheep

Section XI: Toxicants that Affect the Skin

Toxicants that Cause Skin Damage by Primary Photosensitization

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Hypericum - St. Johnswort

Hypericum perforatum - St. Johnswort, klamath weed, goatweed, amber, goats beard, Tipton weed, Eolaweed, Pennyjohn, raisin rose, herb john, commock
H. punctatum
H. concinnum

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Damage by Primary Photosensitization
Herbivores	Within 24 hours to weeks	Days to weeks; rarely lethal	

Family - Hypericaceae (St Johnswort family)

Description

- *Hypericum perforatum*.
    - Plant - Perennial herb, erect, 1 - 2.5 feet high.
    - Stem - Main stems are usually clustered, woody below, many lateral, opposite branches, slender, produces runners from the base, glabrous, dark rings about the nodes, 2-edged.
    - Flowers - Numerous, deep yellow, leafy, flat-topped, petals, numerous with black dots on margins, stamens numerous, sepals, 5, lanceolate, acute, 5 - 7 mm long.
    - Fruit - 3-valved capsule with numerous seeds. Seeds are cylindrical, slightly pointed at ends, dark brown, mottled with rows of minute depressions, shiny and barely 1 mm long.
    - Rootstock - Underground rhizome.
    - Tiny translucent spots visible on leaf surfaces, when the leaf is held toward a light (thus the species name "perforatum").

Habitat

Europe, now naturalized in most of North America, especially troublesome in the western USA from Oregon to California and the plains states. Roadsides, overgrazed pastures, abandoned fields, open woods, sandy or infertile soils.

Toxic Principle

Hypericin, a fluorescent pigment which is a dianthrone derivative.

Susceptible Species

- Cattle, sheep, horses, goats, rabbits.
- Especially breeds with large areas of unpigmented skin.

Toxicity

- Sheep.
    - Consumption of approximately 5% of the body weight may produce toxicosis.
    - Readily grazed when succulent.

- Cattle.
    - Consumption of approximately 1% of the body weight may produce toxicosis. Partially detoxified by drying.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanism of Action

- Hypericin remains intact upon ingestion, is absorbed and passes through the liver; the liver remains undamaged.
- The hypericin, therefore, reaches the general circulation and cutaneous structures.
- Molecular oxygen is required for reactions in the skin which cause the photosensitive reaction.
- There is no accumulation of phylloerythrin in St. Johnswort poisoning.
- Ordinarily glass or a layer of water will not protect against St. Johnswort photosensitization, which differentiates it from sunburn.

Signs

- Signs appear within 24 hours of ingestion.
- Increased respiration, heart rate and body temperature.
- Slight diarrhea, marked salivation.
- Mild dermatitis, pruritis, ulceration.
- Affected animals may immerse themselves in water.
- May be hyper-reactive to cold water.
- Convulsions and death may occur after ingestion of large quantities, but this rarely occurs on pasture.
- With the more common and chronic syndrome, the primary signs include: severe erythema of the conjunctiva and buccal mucous membranes, blindness, feed refusal and death due to starvation.

Diagnosis

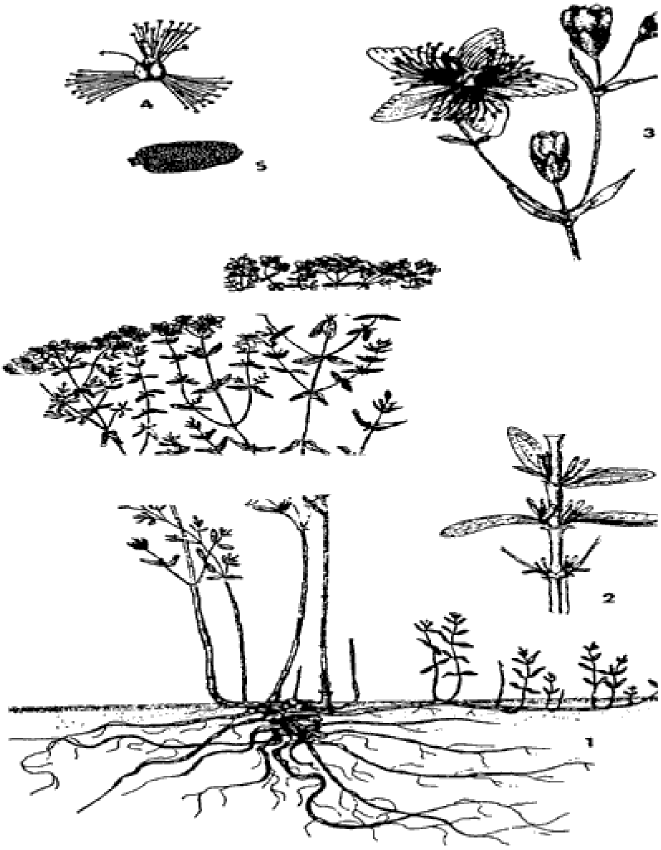
Identification of *Hypericum*, evidence of consumption and accompanying (appropriate) clinical signs and lesions.

Treatment

- Keep in shade, pasture at night away from source of plant.
- Supportive care.

Comment

Black-skinned animals are rarely affected with photosensitization of any type. In St. Johnswort poisoning of Holstein cattle, the black pigmented areas were unaffected while the skin of white areas was inflamed and large sloughs occurred.



St. Johnswort, *Hypericum perforatum* L. - **1**, plant in flower; **2**, portion of stem with leaves; **3**, flower and buds; **4**, stamens and ovaries; **5**, seed. **Perennial**, reproducing by seeds and rootstocks. **Root** system branched and extending to considerable depth. Shallow, short rootstocks extend out several inches from crown. **Stems** smooth, branched, erect, somewhat 2-edged, 1 to 2 feet (30 to 60 cm) tall, woody at base. **Leaves** opposite, elliptic to oblong, covered with small clear dots. **Flowers** about 3/4 inch (1.9 cm) in diameter, 5-petaled, orange-yellow with occasional black dots along edges of petals. **Seed pods** rounded, pointed, with 3 parts and many seeds. **Seeds** about 1/16 inch (1.5 mm) long, cylindrical, blackish, shiny with a rough, pitted, resinous surface. **Found** in pastures, meadows, rangelands and along roadsides. Not relished by grazing animals; may cause skin irritation and loss of condition in livestock, especially white animals. Also commonly known as Klamath weed.

Common St. John's-Wort (*Hypericum perforatum* L.)

Family - St. John's-wort (Hypericaceae).
Growth Form - Perennial herb from fibrous roots.
Stems - Upright, branched, smooth, sometimes slightly woody at the base, up to 2 feet tall.
Leaves - Opposite, simple, oblong, black-dotted, without teeth, smooth, up to 3/4 inch long.
Flower Arrangement - Flowers many, in terminal cymes.
Flowers - Yellow, up to 1 inch across.
Sepals - 5, green, pointed.
Petals - 5, yellow, black-dotted along the edges, free from each other.
Stamens - Usually 3 groups of five.
Pistils - Ovary superior; styles 3.
Fruits - capsule ovoid, about 1/4 inch long, many-seeded.
Habitat - Fields, pastures, roadsides.
Range - Throughout the state.
Time of Flowering - June to September.
Associated Plants - Common milkweed (*Asclepias Syriaca*), Fleabane (*Erigeron Strigosus*), white prairie clover (*Melilotus alba*), and field goldenrod (*Solidago nemoralis*).

Spotted St. John's-Wort (*Hypericum punctatum Lam*.)

Family - St. John's-wort (Hypericaceae).
Growth Form - Perennial herb.
Stems - Upright, sometimes woody at the base, smooth, up to ? feet tall.
Leaves - Opposite, simple, oblong to broadly lanceolate, rounded to pointed at the tip, rounded at the base, black-dotted, without teeth, smooth, up to 3 inches long, without a stalk.
Flower Arrangement - Many flowers in terminal cymes.
Flowers - Yellow, about 1/2 inch across, borne on short stalks.
Sepals - 5, green, free to the base, pointed at the tip.
Petals - 5, yellow. Black-dotted throughout, more or less rounded at the tip.
Stamens - Many, grouped together in sets of 5.
Pistils - Ovary superior; styles 3.
Fruits - Capsule ovoid, about 1/4 inch long.
Habitat - Roadsides, fields, and woods.
Range - Throughout the state.
Time of Flowering - July and August.
Associated Plants - Milfoil (*Achillea millefolium*), black-eyed Susan (*Rudbeckia hirta*), and tall goldenrod (*Solidago can? densis*).

Fagopyrum - Buckwheat

Fagopyrum esculentum - *F. sagittatum, Polygonum fagopyrum*, Buckwheat

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Damage by Primary Photosensitization
Herbivores	Within 24 hours to weeks	Days to weeks, rarely lethal	

Family - Polygonaceae (buckwheat family)

Description

- Plant - Small grain crop, annual.
- Leaves - Triangular, heart-shaped, with semicylindrical sheaths.
- Flowers - 8 honey-bearing yellow glands; calyx is petal-like and equally 5-parted; stamens - 8, styles - 3, racemes of white, greenish or rose- colored flowers.
- Fruit - Achene, acute and entire, smooth and shiny, 3-sided.

Habitat

- Europe; northeastern USA.
- Cultivated, seeds are used in human diet, and whole plant is fed to stock.
- Also planted as ground cover, for green manure and occasionally as a forage plant.
- Used in pancake flour for human use.

Poisonous Principle

- The poisonous principle is still the subject of some debate. It is most often asserted that toxicity is due to a fluorescent substance, the naphthodianthrone derivative fagopyrin. It has, however, also been suggested that a fungal metabolite may be involved.

Susceptible Species

All livestock with unpigmented skin. Humans are more often affected with allergy than photosensitization.

Toxicity

- All parts are capable of producing photosensitization in livestock.
- Moderate to large quantities of dry or green plant or seed may cause photosensitization.
- White Yorkshire pigs from 3 months of age to old brood sows developed signs in 24 hours after being placed on a flowering buckwheat field.

Signs and Lesions

- Signs may appear from 24 hours to several weeks after the first ingestion.
- In acute cases, nervous signs also may occur.
- "Fagopyrism" is the name given to the photosensitivity caused by buckwheat.
- Inflammation and swelling, especially about the ears, face and eyelids.
- Itching, sloughing.
- In severe cases, inflammation may spread to unpigmented areas of the skin and vesicles may develop containing a yellowish fluid.
- Ruptured vesicles form a yellow or brown crusty scab.
- Erythema is followed by subdural edema and eventual necrosis.
- Nervous signs in acute cases include excitement, running about, grunting, squealing or bellowing, jumping, convulsions and prostration.
- *Fagopyrum* appears to be a primary photosensitizer. However, in a few instances liver damage has been mentioned.

Diagnosis

Identification of *Fagopyrum*, evidence of consumption, and appropriate signs and lesions.

Treatment

Prevent access and keep in shade.

Fagopyrum

Cymopterus - Spring Parsley

Cymopterus watsonii - Spring parsley
C. longipes

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Damage by Primary Photosensitization
Sheep, cattle, birds	Within 24 hours to weeks	Days to weeks, rarely lethal	

Family - Rutaceae family (carrot family)

Description

- Perennial grows 4 - 6 inches tall.
- Leaves - Finely divided, resemble parsley.
- Flowers - Small, white or cream-colored in umbrella-like clusters about 1 inch across.
- Root - Long taproot.

Habitat

C. watsonii grows in an area extending from southeastern Oregon and southwestern Idaho throughout Nevada to southwestern Utah.

Toxic Principle

- Believed to be due to one or more photoactive furocoumarins (psoralens) previously identified in genera of the carrot family.
- Parsley, carrots, parsnips and other members of the carrot family have produced photosensitivity in man.

Susceptible Species

Sheep and cattle. Chicks have been affected experimentally by the feeding of seeds. Ducklings have also been experimentally affected.

Toxicity

- The photoactive compound is in the leaves and seeds of the parsley but not in stems and roots. This is the case in other members of the carrot family.
- Photosensitivity has been produced both orally and topically with no major increases in liver enzymes and no liver changes on histologic examination in dosed chicks.
- Most poisonings in sheep are from March to May.

Signs

- "Sunburn" varies from slight to severe.
- Blisters on sheep's bodies not covered by wool.
- Losses primarily occur in lambs (often high losses) because the udders and teats are so painful that ewe will not permit lambs to nurse.
- Surviving lambs often stunted from lack of milk.
- Cattle - Unpigmented area affected: possible blisters and rapid weight loss in adults.
- Cows also refuse to let calves nurse due to teat lesions, but calf losses are usually low.

Recovery

Gradual recovery on withdrawal.

Treatment

- Shade, remove from source.
- Supplemental feeding, especially lambs and calves.
- Supportive care for skin lesions if animals are amenable to being handled.

Prevention

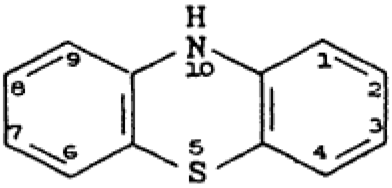
- Keep off range with spring parsley in early spring.
- Use of 2,4-D to control plant.

Phenothiazine (Thiodiphenylamine)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Damage by Primary Photosensitization
Calves, goats, sheep, fowl (horses are sensitive to penothiazine but apparently do not develop photosensitization)	Days	Days to weeks; potentially lethal	

Sources

- Phenothiazine is very insoluble in water and although stable when dry, is readily oxidized when wet. Due to the insolubility of phenothiazine in water, it is formulated in suspensions and if not shaken well prior to dosing, the drug will be unevenly distributed to the animals.
- Phenothiazine is also available in powdered form for addition to the feed or incorporation into salt, mineral or combined salt-mineral mixes, which are used either by addition to feed or as salt licks. The powdered phenothiazines are generally used for prophylaxis (depressed egg production by female worms in the intestine results from continuous low level medication) as an adjunct to regular deworming treatments.
- In earlier years, powdered phenothiazine was generally administered to horses in dry ground feed on a continuous, daily basis. There are reports of continuous dosing of individual horses for 5 - 10 years at up to 5 g/day without untoward effects and without development of resistance in the parasite. This procedure is still practiced in the UK. The primary reason for the widespread, continued use of phenothiazine in the horse is its efficacy against small strongyles.
- Chickens and turkeys are treated with phenothiazine to remove the cecal worm, *Heterakis gallinarum*. Fowl are most often treated monthly by addition of the drug to the feed.



Phenothiazine

Toxicity

- The toxicity of phenothiazine has limited its use in swine and altogether prevented its use in the dogs, cats and human beings. It is used in ruminants, horses and fowl. The problem in small animals is reportedly severe CNS depression.

- Deaths among sheep from phenothiazine toxicosis are rare. Sheep in good condition will tolerate single doses of 160 grams or continuous dosing with 10 g daily for 49 days without side effects. However, sheep in poor condition may succumb to doses as low as 5 grams.
- Although sometimes formulated with trichlorfon, generally phenothiazines should not be used with organophosphorus compounds due to potentiation of the toxicity of the insecticide.
- Similarly, healthy cattle tolerate 250 g doses of phenothiazine or 3 successive daily doses of 100 g without illness. However, debilitated, anemic cattle are even more susceptible than similarly debilitated sheep. An important toxic effect of phenothiazine in animals in poor condition is hemolysis which compounds an existing anemia in some such animals resulting in death.
- Phenothiazine toxicosis and death has occurred more in horses than in other domestic animals. Most toxicoses have occurred in debilitated and anemic horses. Generally, a toxic dose is above 50 g for an adult horse and above 30 g for a young horse. However, 28 g has caused death in a debilitated adult horse, while 500 g has been tolerated by horses in good condition.
- Obviously, the use of phenothiazine in cachexic animals can be hazardous and other safer drugs should be used when possible, especially when the animals are anemic and emaciated.

Absorption, Distribution, Metabolism and Excretion (ADME)

- It is believed that phenothiazine is converted to phenothiazine sulfoxide by cellular enzymes of the intestinal epithelium. In sheep, some phenothiazine is absorbed intact. After absorption, phenothiazine is further oxidized in the liver, primarily to leucophenothiazine and leucothionol, 2 colorless substances which are excreted in the urine. Upon further oxidation in the atmosphere, these compounds form the brown-red dyes, phenothiazine and thionol. Urine and milk are, therefore, discolored for several days. The presence of these dyes is not, however, indicative of toxicosis.
- Constipation in the treated animals causes retention of phenothiazine and, thereby, increases absorption from the intestine, increasing the probability of toxicosis.

Signs

- Signs of phenothiazine toxicosis in the horse include dullness, weakness, anorexia, and possibly oliguria, colic, constipation, fever and rapid pulse. Hemolytic effects include icterus, anemia and hemoglobinuria.
- Photosensitization may accompany administration of phenothiazine when animals are subsequently exposed to bright sunlight. Photosensitization occurs especially in calves but may also occur in goats, sheep and fowl but not horses.
- When the dose of phenothiazine is sufficiently high, not all the phenothiazine sulfoxide is converted to leucophenothiazine and leucothionol by the liver. Calves are apparently less adept at this conversion than older cattle or sheep. A portion of the phenothiazine sulfoxide diffuses into the aqueous humor. On exposure to sunlight, photochemical reaction results in keratitis and often corneal ulceration within 36 hours. Bright sunlight reflected from snow cover has commonly resulted in phenothiazine associated corneal ulcers in calves.
- Non-pigmented areas of the skin may be reddened, especially commonly affected are the ears, muzzle and other parts of the face. Shaking of the head, rubbing of the ears and other signs of irritation may be seen.
- There was a slight increase in abortion in ewes given phenothiazine at 3 weeks before the end of gestation. Generally, phenothiazine is contraindicated only during the last month of gestation. Phenothiazine discolored milk can generally be regarded as safe for feeding other animals.
- Permanent staining of wool or haircoat may result from phenothiazine excreted in the urine or from spilling the drench on the animal.

Treatment

- Toxicosis can be reduced by the use of smaller doses in weakened animals, although these may be only partially effective in parasite removal.
- For acute overdose, a saline cathartic combined with activated charcoal is used to reduce absorption and hasten removal from the gut.
- Treatment of phenothiazine toxicosis in the horse is primarily intended to replenish lost red cells via blood transfusion. Fluids and bicarbonate may lessen the likelihood and severity of renal tubular damage due to hemoglobin released from red cells.

Toxicants that Cause Skin Effects other than Photosensitization

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1. Metal that Affect the Skin

Thallium

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
All species; esp. dogs	Hours to weeks	Weeks to months; very often lethal	

Please review the chapter in: Osweiler GD. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Kendall/Hunt Publishing Company, 1984. - Available from amazon.com -
These notes are intended only to supplement that chapter.

Sources

- Rodenticide or insecticide formulations in the form of syrups, jelly or pastes. Often applied to foods such as cookies, cakes, peanut butter or grain.
- Commercial preparations, such as ant traps, ant baits and rat poisons generally contain 0.5 - 1.0% thallium.
- In 1963, the federal government adopted legislation prohibiting the sale of thallium containing pesticides to the general public.
- In commercial applications, thallium has been largely replaced by other rodenticides such that, at the present time, thallium is infrequently used in the USA but is still commonly used in some countries.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Thallium is absorbed through the skin and from the digestive tract.
- The concentration of thallium in the kidney may be much greater than in other tissues.
- Because of its comparatively slow excretion, thallium may be a cumulative poison if exposure is repeated or continuous.
- The biological half-life is approximately 3 - 8 days.
- During the first day after exposure, the kidney is the main route of excretion and urinary concentrations of thallium are high. Later, the concentrations in feces are approximately twice as high as urinary levels.

Toxicity

- Generally considered a cellular poison.
- LD_{50} = 10 - 15 mg/kg.
- Lethal dose 20 - 25 mg/kg.
- Will accumulate in body.

Mechanism of Action

Combines with mitochondrial sulfhydryl enzymes, causing an interference with oxidative phosphorylation. Inhibits aerobic metabolism in skin, brain, and kidney. Will exchange for potassium in muscle and nerves.

Diagnosis

- Confirmation of the diagnosis may be possible in some instances by means of laboratory confirmation (atomic absorption spectroscopy) of thallium in urine, feces or kidney.
- Any thallium in body is generally considered significant, although with increasingly sensitive methods of detection, this might change.

Clinical Signs

- Acute (within 1 - 4 days of ingestion) - gastric distress, vomiting, severe hemorrhagic diarrhea, abdominal pain, and anorexia. Lingual ulcers have been reported in cats. Motor paralysis and trembling may occur.
- Subacute - signs appear within 3 - 7 days. Gastric distress and motor disturbances are similar but are more mild. Prominent skin changes occur. Erythema and pustule formation (usually begins on nose and ears, can progress to axillary region and torso). Mucopurulent ocular discharge may occur. Alopecia and encrustation of skin can occur.
- Chronic - may take 7 - 10 days. Alopecia and drying and scaling of skin can occur 1 - 3 weeks postingestion.

Treatment

- Emesis may be indicated for very recent exposures.
- Prussian blue is the preferred agent to enhance the elimination of thallium. Prussian blue is a nonabsorbable lattice of potassium ferric furocyanide. It is not absorbed orally. In theory, the potassium is released and mobilizes intracellular thallium, which is then bound by the lattice structure remaining in the gut. Prussian blue has been shown to lower the thallium concentration in the brain of rats. The use of Prussian blue in human thallium toxicosis has demonstrated favorable clinical improvement correlated with increased fecal excretion of thallium. The soluble form of Prussian blue is most effective in adsorbing thallium. Prussian blue is given orally. In humans, 2 - 500 mg capsules are given orally 3 times a day (TID), depending upon the severity of the case, for 2 - 3 weeks. In severe thallium toxicosis, Prussian blue solution has been recommended at 1,000 mg TID (also in man) via a duodenal tube, because of pyloric spasm and gastric dilatation which may accompany thallotoxicosis. The effectiveness of Prussian blue may be lost in patients not able to evacuate the bowel due to constipation and/or absence of intestinal motility. Therefore, mechanical removal of feces may be necessary before administration of Prussian blue. Prussian blue is available through Aldrich Chemical Co.; 940 West Saint Paul Ave., Milwaukee, WI 53233, USA.
- Forced diuresis should be considered as an adjunct to Prussian blue therapy.
- *In vitro* absorption studies have shown equal affinity for thallium (Lehmann PA, Favari L. Parameters for the adsorption of thallium ions by activated charcoal and Prussian blue. J Toxicol Clin Toxicol 1984; 22:331-339. - PubMed -). *In vivo* findings have shown that activated charcoal and Prussian blue are effective antidotes for the treatment of acute thallium intoxication.

Selenium

(See also *Clinical and Diagnostic Veterinary Toxicology* as well as *Astragalus/Oxytropis* section of these notes)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Most species	Chronic	Chronic; often lethal	

Sources

- **Obligate indicator plants** - require Se in large amounts for growth. Therefore their presence indicates high selenium soils are present. These plants concentrate 100 - 10,000 ppm Se.
    - Examples include:
        - *Xylorrhiza* = woody aster.
        - *Oonopsis* = goldenweed.

        - *Stanleya* = prince's plume
        - *Astragalus* = locoweed.
- The selenium is in a water soluble form in seleno amino acid analogs of cysteine and cystathionine.
- **Facultative indicator plants** - absorb Se if present in high concentrations, but do not require large amounts for growth. These are, therefore, found in both seleniferous and non-seleniferous soils. If not seleniferous soils, they may concentrate 25 - 100 ppm of Se.
    - Examples include:
        - Other asters.
        - *Atriplex* = saltbrush.
        - *Sideranthus*.
        - *Machaeranthera*.
- **Non-accumulator plants** - such as crop plants when grown on seleniferous soils may also accumulate 1 - 25 ppm Se as part of their protein make-up in integral proteins (i.e., seleno-cystine, selenocysteine, selenomethionine and selenocystathionine) in a water insoluble form. Forages and grains from seleniferous areas may be more palatable than those from other sources.
- High selenium soils and plants are known to exist in western Canada, Arizona, Colorado, the Dakotas, Idaho, Kansas, Nebraska, Nevada, New Mexico and Utah.
- Other sources include errors in feed formulation which are rare.
- Mine wastes, especially from copper, silver and high sulfide ores.
- Iatrogenic administration of excessive doses of selenium intended as therapy or prevention of musculoskeletal disorders.
- Selenium levels are highest in low rainfall areas with alkaline soil.
- Leaching of selenium from the soil as a result of irrigation and transport downstream to evaporation basins has resulted in widespread teratogenesis in water fowl.

Toxicity

- **Requirement**. Most domestic animals require selenium in their diet. For food-producing species, a level of 0.3 ppm in the total diet is often recommended.
- **Acute selenosis**.
    - Ingestion of obligate indicators (400 ppm Se).
    - One to 5 mg Se/kg BW orally is acutely toxic.
    - Parenterally 0.2 mg Se/kg BW is acutely toxic.
    - LD_{50} in sheep of intramuscularly administered selenium 0.7 mg Se/kg BW.
    - Single minimal lethal doses of oral sodium selenite. Horse 3.3 mg/kg, cattle 10 mg/kg, swine 17 mg/kg.
- **Subacute selenosis of swine**.
    - Sodium selenite at 25 ppm (of selenium) in the diet.
    - Alkali disease (chronic toxicosis) in livestock exposed to Se at 5 - 40 ppm in the diet.

Mechanism of Action

- Possibly due to glutathione depletion and secondary lipid peroxidation.
- Probably not due to sulfhydryl enzyme inhibition.

Signs and Lesions

- **Acute selenosis** - due to ingestion of obligate indicator plants or iatrogenic toxicosis after parenteral administration.
- All species are susceptible-onset of clinical signs within 1 - 2 hours; death 2 hours to 7 days later.
    - Clinical signs include:
        - Lethargy, nonresponsiveness.
        - Dyspnea, cyanosis, nasal discharge.
        - Teeth grinding.
        - Anorexia.
        - Prostration.
        - Mydriasis.
        - Elevated temperature.
        - Incoordination.
- Lesions.
    - Edematous lungs, hydrothorax, pale heart.

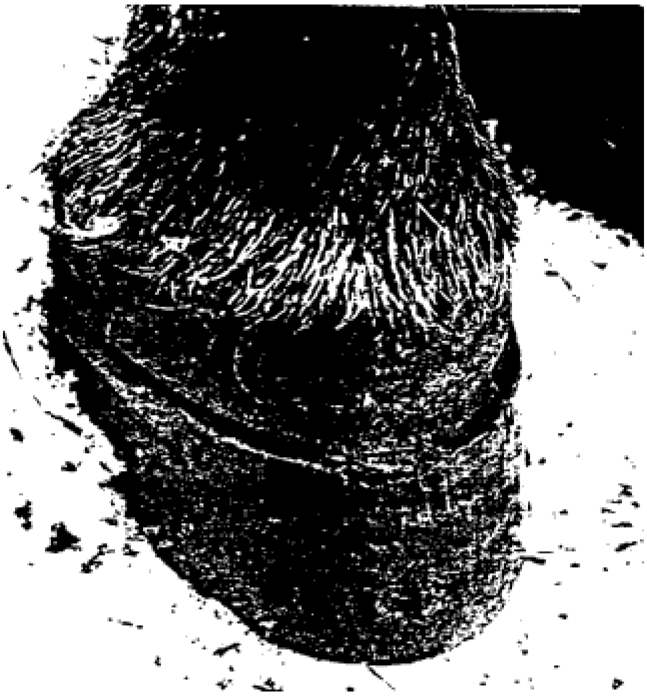
- **Subchronic selenosis**.
    - Subchronic selenosis does occur in swine. Sodium selenite in the diet at 20 - 25 ppm selenium will produce focal symmetrical poliomalacia after several weeks.
    - Quadriplegia with flaccid paralysis.
    - Sternal recumbency.
    - Ataxia initially.
    - Some coronary band separation.
    - Some alopecia.
    - Blind staggers in large animals (in the past thought to be due to subchronic selenosis) associated with the ingestion of moderate amounts of obligate or facultative indicator plants over a period of weeks has not been reproduced by feeding selenium salts. Moreover, experimental work with *A. bisulcatus* in cattle produced loco lesions (neurovisceral cytoplasmic vacuolation) and similar clinical signs.
- **Chronic selenosis**.
    - Alkali disease (chronic selenosis) in livestock is due to the ingestion of nonaccumulator plants grown on seleniferous soils (5 - 40 ppm selenium) over a period of weeks or months.
    - Primarily seen in cattle and horses.
    - Signs and lesions.
        - Decreased vitality.
        - Anemia.
        - Joint stiffness.
        - Lameness.
        - Rough hair coat.
        - Hair loss (tail and mane).
        - Horn and hoof deformities (circular break in hoof below coronary band).
        - No anorexia (often graze on knees).
        - Hair loss precedes hoof changes.
    - Lesions: cardiomyopathy and liver cirrhosis.
- **Teratogenesis in waterfowl and poultry**.
    - Underdeveloped feet, legs.
    - Missing or underdeveloped lower or upper beak.
    - Missing or underdeveloped eyes.

Diagnosis

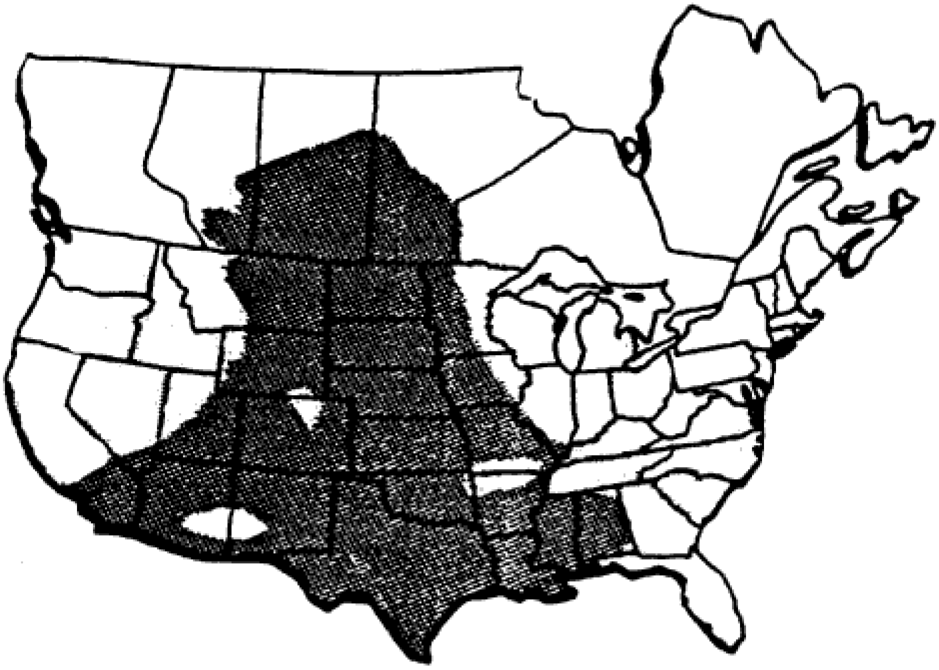
- Appropriate clinical signs and lesions.
- Access to a toxic dose of selenium.
- Whole blood selenium.
- Liver selenium
- Appropriate lesions on gross and histologic examination.

Treatment

- **Acute selenosis**.
    - Terminate exposure; minimize absorption (if recent oral exposure).
    - Symptomatic therapy (diuretics).
    - Acetylcysteine: loading dose 140 mg/kg IV followed by 70 mg/kg IV QID
- **Chronic selenosis**.
    - Dilute diet with feed low in selenium.
    - Increase protein content of ration (SH groups).
    - Increase linseed meal content of ration.
    - Adding organic arsenic to diet to increase biliary excretion has been suggested for poultry, cattle, and pigs; although such an approach has not been recommended for horses.
    - Pretreatment with copper can be protective against selenium toxicity.



Horizontal hoof-wall cracks characteristic of chronic selenium poisoning (alkali disease).



Approximate geographic distribution of seleniferous soils in North America (shaded areas) based on plant selenium levels in excess of 0.1 ppm. Marginal seleniferous soils are indicated by light shading.

Molybdenum Toxicosis - Copper Deficiency

(Supplements *Clinical and Diagnostic Veterinary Toxicology*; see also *Copper Toxicosis* section of these notes)

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Ruminants	Days to week	Days to chronic; often lethal	

Sources

- Molybdenum toxicosis is most often seen in ruminant animals.
- Usually a concomitant copper deficiency is also present.
- The molybdenum concentration of forage can be unusually high when:
    - There is a naturally high content of Mo in the soil (e.g., Florida, Oregon, Nevada and California).
    - Molybdenum is added to fertilizers to increase nitrogen fixation in legumes.
    - Industrial contamination of pastures occurs in the vicinity of mining or metal alloy production plants.

Toxicity

- Cattle are more susceptible than sheep and young animals are more susceptible than old.
- Problem in cattle when the dietary Cu:Mo ratio is less than 2:1.
- Problem in sheep when the dietary Cu:Mo ratio is less than 1.1 - 4.1:1.
- High dietary sulfate concentrations exacerbate the condition.

Mechanism of Action

- Debatable or controversial: Mo forms an *in vivo* complex with dependent copper.
- May actually just be a depletion of copper enzymes such as:
    - Ceruloplasmin (Fe absorption, mobilization and utilization).
    - Lysyl oxidase - amine oxidase (elastin of vessels and polypeptide chains in bone collagen).
    - Tyrosinase (melanin production).
    - Cytochrome C oxidase (energy for phospholipid synthesis in myelin).
    - Dopamine-ß-hydroxylase.

Signs and Lesions

- Typical bovine syndrome.
    - Morbidity may approach 80%.
    - Onset 8 - 10 days after being put on a pasture high in molybdenum.
    - Clinical signs.
        - Diarrhea with gas bubbles.
        - Emaciation.
        - Decreased milk production.
        - Decreased fertility and libido.
        - Lameness.
        - Anemia (microcytic, hypochromic).
        - Achromotrichia.
    - Chronically - Bone fractures.

Lesions

- Osteoporosis, bone fractures.
- Sheep syndrome.
    - Enzootic ataxia (reported in Australia).
    - Ewes - Stringy depigmented dark wool with loss of crimp, anemia.
    - Lambs - Ataxia, blindness.

Treatment

Copper supplementation either as Cu SO$_4$ in feed or as copper glycinate injections. Be especially careful when supplementing copper intake in sheep (see section on copper toxicosis).

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2. Other Organic Compounds that Affect the Skin

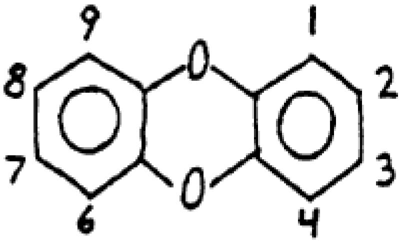
Polychlorinated Dibenzodioxins, Highly Chlorinated Naphthalenes and Related Halogenated Aromatics

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Highly Chlorinated Naphthalenes	All species	Chronic	Chronic, potentially lethal, toxicoses rare in domestic species	
Related Halogenated Aromatics	All species	Chronic	Chronic, often lethal, toxicoses rare in domestic species	

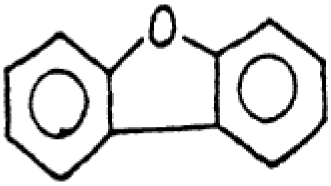
Dioxins - The term dioxin is commonly used to denote compounds that are actually polychlorinated dibenzodioxins and, much less often, other polyhalogenated dibenzodioxins).
Dibenzofurans - The term dibenzofurans is used to denote polychlorinated dibenzofurans and other polyhalogenated dibenzofurans).
Azoxybenzenes.
Azobenzenes.
Highly Chlorinated Naphthalenes.

Sources

- Dioxin and dibenzofuran contaminants are often in waste oils from chlorophenol plants, for example, from the manufacture of:
  - Trichlorophenol.
  - Pentachlorophenol.
  - Hexachlorophene.
- **Note** - In 1974, 200 x 10^6 lb of chlorophenols were produced by the chemical industry.
  - Contaminants in a deliberately produced chlorophenol generally include other chlorophenols, chlorobenzenes, and chloronitrobenzenes. For example, contaminants of pentachlorophenol include hexachlorobenzene, octachlorodibenzodioxin, and hexachlorodibenzodioxin.
  - Contaminants may also be present in chlorophenol-derived products and related compounds; such as 2,3,7,8-tetrachlorodibenzodioxin (TCDD) in the herbicide, 2,4,5-T (part of Agent Orange). Potential dioxin contaminants may also occur in the organophosphorus insecticide ronnel and the benzoic acid herbicide dicamba.
  - Environmental pollutants may be released as a result of accidents at chlorophenol plants. For example, a spontaneous exothermic reaction producing dioxins can be initiated when system pressure and heat are excessive.
  - Combustion - Low level contamination.
  - Leather processing wastes and leather meal used in swine and other feeds may contain toxic amounts of hexachlorodibenzodioxins from pentachlorophenol.
- Highly chlorinated naphthalenes.
  - Lubricating oils, greases, insulating materials, wood preservatives (old products - no longer added to oils and greases).
- These and other environmental contaminants are potentially present in hazardous waste dumps, and have been spread about by disreputable waste haulers.



Dibenzodioxin



Dibenzofuran

Toxicity

- By far, the most toxic of these compounds is 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD). This compound has never been produced on purpose but has accidentally been produced as a true contaminant in the manufacture of trichlorophenol and the herbicide, 2,4,5-T. This herbicidal compound was half of the formulation used in Agent Orange which was applied in Southeast Asia during the Vietnam War.
    - The single oral dose LD_{50}s for 2,3,7,8-TCDD are:
        - Guinea pigs - 0.6 µg/kg.
        - Monkeys - 50 - 70 µg/kg.
        - Mice - 284 µg/kg.
- Because of the extreme sensitivity of mammals and birds to this compound, samples must be analyzed by methods with a sensitivity for TCDD in the area of 0.01 ppb. The 2,3,7,8-TCDD isomer is 3 - 100 times as toxic as other TCDDs. Other dioxins vary widely in toxicity, therefore specific identification of particular dioxins is essential. Unfortunately this process is extremely expensive, and few laboratories have the necessary equipment and/or expertise to perform these procedures.
- TCDDs can cause immunosuppression with exposure at levels too low to produce clinical or pathological changes. The principle effects are on T-cells. B-cells and, therefore, humoral immunity are not greatly affected.

Mechanism of Action

- It is believed that the compounds bind to a cytosolic enzyme, which is transferred into the nucleus and thereafter triggers gene expression, causing induction of mixed function oxidase enzymes and "other toxic effects." The affinity for the binding of the cytosol proteins and the tendency to induce mixed function oxidase enzymes tends to parallel the acute toxicity of the different compounds.
- Interference with heme metabolism and build-up of porphyrins have been associated with some of the dermal lesions observed.
- See the following handout on PCBs and PBBs (Mechanism of Action section).

Signs and Lesions

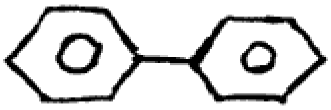
- Laboratory animals.
    - Chronic weight loss.
    - Skin lesions (often hyperkeratosis).
    - Liver damage.
    - Mutagenesis.
    - Carcinogenesis (primarily liver and oral tumors).
    - Teratogenesis.
        - Cystic kidneys and cleft palate in mice.
        - Absence of eyelids in hamsters
    - Fetotoxicity.
        - Gastrointestinal hemorrhage in rats.
        - Overgrowth of renal papillae.
        - Thymic atrophy.
        - Fatty liver.
        - Generalized edema.
        - Low birth weight.
        - Fetal resorption.

    - Embryolethality.
    - Death.
- Mice - Behavioral effects.
    - Hyperirritability, aggressiveness, restlessness.
- Cats and dogs.
    - Chronic weight loss.
    - Chronic respiratory infections.
    - Oral and nasal lesions.
    - Hair loss.
    - Centrilobular hepatic degeneration.
    - Renal tubular degeneration.
- Cattle.
    - Weight loss and emaciation.
    - Splenic atrophy.
    - May eat normally but feed conversion extremely poor.
    - Drop in milk production.
    - Hydropic degeneration in kidney.
    - Hypertrophy of all squamous epithelia, including the skin.
- Horses (in contact with heavily contaminated soil).
    - Chronic anorexia.
    - Listlessness.
    - Rapid loss of weight, emaciation with serous atrophy of fat.
    - Weakness and unsteady gait.
    - Subcutaneous edema.
    - Hair loss, especially of the mane and tail; hair may fall out in clumps.
    - Skin and oral ulcerations and fissures, resulting in alligator-like skin.
    - Lymphoid atrophy.
    - Conjunctivitis.
    - Polydipsia.
    - Colic.
    - Severe laminitis, with inflammation of the sole and frog.
    - Liver enlargement up to 3 times normal size.
    - Hepatic portal cirrhosis, biliary proliferation, fibrosis around central vein.
    - Hypogammaglobulinemia.
    - Ascites.
    - Icterus.
    - Diarrhea, tarry feces.
    - Hematuria.
    - Some mares develop thick "stallion-like" necks.
    - Failure to conceive.
    - Abortion, usually with the fetus presented dead.
    - Death in foals.
    - Gastric ulcers.
    - Pulmonary hemorrhage, edema and bronchopneumonia.
    - Death in adults.
- Chickens and turkeys.
    - Hydropericardium.
    - Edema.
    - Ascites.
    - Endothelial proliferation.
- Monkeys.
    - Severe weight loss.
    - Blepharitis, periorbital edema.
    - Loss of fingernails and eyelashes.
    - Facial alopecia.
    - Acneform eruptions.
    - Mild anemia.
    - Thrombocytopenia.
    - Lymphopenia, lymphoid atrophy, especially thymic atrophy.
    - Increased relative weights of liver, kidney and adrenal.
    - Ascites.
    - Gangrenous necrosis of the phalanges.

    - Irregular estrous cycles, decreased fertility.
    - Embryotoxicity.
    - Abortion and stillbirth.
  - Humans (accidentally exposed workers).
    - Chloracne.
    - Liver damage.
    - Polyneuropathy especially affecting the legs; decreased conduction velocity confirmed on EMG; but with no lesion.
    - Weakness and pain in legs.
    - Somnolence or insomnia.
    - Psychiatric disorders.
    - Sexual dysfunction.

Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs)

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Polychlorinated Biphenyls (PCBs)	All species	Chronic	Chronic; potentially lethal, toxicose rare in domestic species	
Polybrominated Biphenyls (PBBs)	All species	Chronic	Chronic; potentially lethal, toxicose rare in domestic species	



Basic Biphenyl Nucleus

Sources

- PCBs.
  - Transformers, other electrical insulators (especially fluids), building materials, old lubricants.
- PBBs.
  - Fire retardant was accidentally mixed in feeds in Michigan.
- Polychlorinated biphenyls (PCBs) are organic compounds which are widely distributed in the environment. Polybrominated biphenyls (PBBs) are similar compounds which are less widespread, but still constitute a chemical hazard.
- Commercially, PCBs and PBBs consist of mixtures of several major and many minor components, the major ones being biphenyl compounds with varying degrees of chlorination or bromination, in some 210 possible halogenation patterns.
- The minor components are contaminants such as brominated naphthalenes and halogenated dibenzofurans or dibenzodioxins.
- In the past, massive quantities of PCBs and PBBs were widely used in industry without much concern over their potential toxic effects.
- These organic compounds are highly stable, nonflammable, lowly volatile, resistant to acids and bases, insoluble in water, and have a high dielectric constant. These characteristics make them useful in heat exchangers and dielectric fluids, hydraulic and lubricating fluids, plasticizers, printing inks, paints, adhesives, duplicating paper, flame retardants, and extenders for pesticides.
- Over 500,000 tons of PCBs were produced in the USA since 1929 and marketed under the trade name Aroclor. Foreign trade names include Clophen, Phenoclor, and Kaneclor.
- Although, the production of PCBs and PBBs was halted prior to 1979, after the potential toxicity of polyhalogenated biphenyls was realized, many PCB and PBB containing products are still in use.
- It is estimated that over 400,000 tons of PCBs have been lost to the environment since 1932.

- Most of these compounds are highly lipophilic, largely resistant to microbial breakdown and biotransformation, and only slightly photodegradable; characteristics which have resulted in intensive bioaccumulation. Persistence depends on the degree and pattern of halogenation. They persist in food chains, aquatic sediments, landfills, and other biological and physical reservoirs. Fish and fish-eating wildlife are the primary biological magnifiers.
- Contaminated feedstuffs are responsible for most exposures of domestic animals. This contamination is often a result of: utilizing fishmeal or recycled animal or paper products in the feed; leakage of lubricants from processing machinery; dissolution of compounds from paints and sealants on silos, water and feed troughs, or storage tanks; availability of insulation or flaking paint in degenerated animal housing; and occasionally from an accidental mixing of PCBs or PBBs in feed or other products offered to livestock. In 1973, the accidental mixing of PBBs instead of magnesium oxide into Michigan livestock feeds resulted in the contamination and destruction of nearly 30,000 cattle, 5,920 hogs, 1,470 sheep, 1.5 million chickens, and massive quantities of animal feed, eggs, and dairy products.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Cattle have been shown to excrete up to 76 ppb PCBs in their milk when fed PCB containing paper products as 30% of their diet.
- Several studies have reported transmission *in utero* or through the milk to feti or nursing offspring of contaminated dams. The fetal fat of cows fed PCBs at 200 mg/day contained 130.6 ppm PCBs as opposed to 0.65 ppm in that of control cows.
- In addition, PCBs were still detected in high amounts 6 months after cessation of the test feed.
- Dermal application of PCBs also results in extremely rapid absorption.
- Species differences exist with regard to relative susceptibility to PCBs and PBBs.
- Among domestic animals, the ranch mink appears to be the most susceptible with a dietary level of only 1 ppm PCB causing decreased litter size and viability of offspring.
- Swine appear to be somewhat tolerant clinically, but high doses elicit effects.
- All species of animals, whether clinically affected or not, can accumulate PCBs and PBBs in their tissues.

Mechanism of Action

- The mechanism of action of even the most studied components of PCB and PBB mixtures are not completely understood.
- In mammals, birds, and fish, most halogenated biphenyls are inducers of hepatic mixed-function oxidases, but the potencies and specificities vary widely. Generally, PBBs appear more potent than comparable PCBs in inducing these enzymes. In contrast, some congeners depress P_{450} activity.
- Toxicity of PCBs and dioxins depends on the chlorination pattern.
- PCBs with chlorines to the outside (flat = coplanar molecules which are therefore similar to 2,3,7,8,-TCDD) bind to the arylhydrocarbon hydroxylase receptor and are translocated into the nucleus where they initiate transcription of a number of proteins - including some P450 enzymes (e.g., "arylhydrocarbon hydroxylase" = Ah) → liver enlarges. Generally, these are also result in chronic weight loss, skin damage (chloracne in people, scaly, scabby lesions in animals), birth defects (crossed bills in birds), and anti-estrogenicity (altered sexuality, sexual function; low milk production).
- PCBs and dioxins with chlorines to the inside (large chlorines interfere with one another causing the molecule to twist the two rings are no longer flat via the same plane, therefore = noncoplanar) tend to be associated with antithyroid, antidopaminergic, and/or estrogenic effects. Their acute toxicity is generally lower than with the coplanar molecules. However, their chronic effects may be significant (some think that they may contribute to decrements in intelligence in children via effects on thyroid during development - partial cretinism - and inhibition of dopamine synthesis/concentrations in the brain).
- Higher doses of the lower halogenated compounds may induce hepatic dysfunction with subsequent abnormalities in heme synthesis that result in accumulation of large quantities of dermatitis-inducing porphyrin.
- Some of these compounds are also known to be acnegenic, and capable of producing hyperkeratosis and hyperpigmentation of the skin in various species.
- Some studies have shown the metabolism of endogenous substances such as steroids and estradiols to be enhanced in liver and skin, but inhibited in the adrenals. A variety of reproductive effects have been seen in numerous species.
- Effects on the immune system are unclear. PCBs have been shown to potentiate duck hepatitis virus in ducklings, induce septicemia in sows, increase disease susceptibility in fish, and reduce the response

of guinea pigs to tetanus toxoid. Gestating sows fed PBBs at 200 ppm of the diet showed a decreased lymphocytic response to mitogen stimulation, however, bacteriocidal activity was not consistently altered. In one study, however, lactating cows exhibited normal immune competence until tissue concentrations exceeded 1000 mg/kg at which time they became moribund.

Clinical Signs

- The toxic response to PCBs differs depending on species, age, sex, and dose with young animals and, oftentimes, females being more susceptible.
- Relatively high concentrations of PCBs or PBBs can accumulate in animal tissues without expression of acute effects or lesions. Nevertheless, chronic biochemical and physiologic changes occur with dietary exposure to feedstuffs containing less than 1 ppm.
- With low level feeding, the usual signs are depressed weight gain and anorexia. Intermittent exposure appears to be more detrimental than constant and/or gradually increasing exposure. In addition, a dose of PCBs administered over time produces more severe effects than the same dose administered acutely.
- Growing swine fed 20 ppm PCBs for 13 weeks showed a slight decrease in weight gain and feed efficiency as compared to controls. In a similar study, a smaller total dose administered within a shorter time (100 ppm for 1 week) resulted in similar but more intense effects during the following 16 weeks. Another feeder pig diet containing PBBs at 200 ppm caused decreases in average daily gain and feed intake to about one-half of control values.
- Depression, septicemia, mummification of feti, and an increase in stillbirths may also occur in swine. Sows fed 20 ppm PCB during gestation and nursing, farrowed and weaned about half as many pigs as control sows.
- In cattle, acute signs of toxicosis do not appear until dietary concentrations approach 5,000 ppm.
- Clinical signs include decreased milk production, anorexia, lacrimation, salivation, dehydration, diarrhea, alopecia, hyperkeratosis, weight loss and terminal recumbency.
- Many of these, especially hyperkeratosis, are also observed in animals suffering from "X disease" which affects cattle, sheep, and swine. This is now known to be caused by highly chlorinated naphthalenes which are frequent contaminants of PCBs.
- Heifers fed 25 g of PBBs per day were anorexic within 4 days and moribund within 33-66 days. With low level exposure, sub-clinical effects may be interpreted as "poor-doers", poor management, and/or nutritional imbalances. However, in some instances of **suspected** PCB or PBB exposure, gross management or nutritional problems have been ignored. This often presents a diagnostic dilemma for the clinician.

Lesions

- Necropsy findings in swine and primates characteristically include gastric irritation and hyperemia. With higher exposures, mucoid hyperplasia and ulceration of the stomach may be present.
- Reproductive effects in cattle include abortions, embryonal resorption, and decreased fertility. Prepartum exposure to PBBs significantly increases fetal birth weight and the subsequent incidence of dystocia. Cows fed 250 mg per day for 180 or 202 days had a 100% incidence of dystocia. In addition, offspring exposed to PBBs *in utero* had significant conception difficulties at puberty.
- Necropsy findings in cattle may include dehydration, marked emaciation, fetal death with cotyledonary necrosis and hemorrhage, greatly enlarged pale kidneys, and dermal hyperkeratosis.
- Occasional findings include mucosal edema and ulcerations of the gastrointestinal tract, especially the abomasum, a thickened gall bladder wall, and thymic atrophy.
- Gross lesions are rarely present at dietary concentrations below 5000 ppm, so that necropsy may fail to indicate actual PCB or PBB poisoning. However, varying amounts of liver hypertrophy occur with either low level chronic exposure or high level acute exposure. The enlargement is not usually severe and is characterized histologically by scattered areas of glycogen depletion, dilatation of sinusoids, fatty degeneration, and very rarely, at higher exposures, centrilobular necrosis.

Effects in Birds

- In birds, PCBs and PBBs initiate clinical signs and lesions somewhat different than those of mammals. "Chick Edema" is now known to be caused by PCBs and their chlorinated naphthalene and dibenzodioxin contaminants. Primary signs and lesions include decreased body weight, anorexia, ascites, subcutaneous edema, dermatitis, hydropericardium, enlarged kidneys, centrilobular hepatic necrosis, splenic atrophy, and occasional enteritis with intestinal hemorrhage. A toxic plant (*Crotalaria*) may cause similar lesions.

- A diet containing 10 - 20 ppm PCBs or PBBs may cause adverse reproductive effects including decreased comb weight in cockerels, decreased fertility and egg production in hens, teratogenesis, reduced hatchability of eggs, and reduced chick viability.
- PCBs have been associated with abnormal sea gull wing development.

Diagnosis

Diagnosis is aimed at detecting PCBs or PBBs in milk fat, body fat, fresh liver samples, feed or other suspected sources. Specimens of milk should be collected in clean (acetone rinsed) glass jars with caps lined with aluminum foil. Tissues may be shipped frozen in (acetone rinsed) aluminum foil. Analysis is usually by gas chromatography with electron capture detection.

Treatment and Control

- There is no specific treatment for PCB or PBB toxicosis. Various agents such as activated charcoal, phenobarbital, vitamin A, vitamin D, and vitamin E, and thyroprotein have been administered without significantly affecting the rate of elimination from the body fat.
- In guinea pigs, ascorbic acid had some therapeutic potential based on its inducement of mixed function oxidases.
- The major goal in control is to discover and eliminate the source of contamination.
- The residue level must be determined in order to calculate the estimated clearance time, and thereby decide whether to decontaminate or destroy the animal.
- In lactating animals, the major route of excretion of these compounds is in the milk fat with a minor fecal component. Three factors affect the resultant half life: **1**) total body fat, **2**) rate and direction of change in the amount of body fat, and **3**) milk fat production.
- Weight loss, parturition, lactation, or other metabolic changes mobilize fat stores and therefore increase the rate of metabolism and excretion of PBBs or PCBs.
- When these compounds are fed, residues tend to reach a steady state within 60 days. Once exposure ceases, there is an initial rapid drop in body fat residues, then a much slower decline.
- The estimated half-lives for PCBs and PBBs for the initial phase are 5.7 and 10.5 days. For the slow phase, the PCB and PBB half-lives are 68 and 60 days (range 33 - 110 days), respectively. After consumption is terminated, there is a nearly constant ratio between milk fat and body fat residues of approximately 0.42:1. The estimated half-life of transmission in eggs is 17 - 28 days.
- These relationships are not valid if exposure is still occurring or during rapid changes in body composition. Furthermore, animals massively exposed and now on a "clean" feed may be continually exposed to a lesser degree from a contaminated environment.
- The long-term residue problems and potential for permanent effects often makes treatment in livestock uneconomical.

Zoonotic Risk

- There is definite evidence of toxicosis in humans chronically exposed to PCBs and PBBs. Some reports have revealed some evidence of carcinogenicity in lab animals. It appears that PCBs are only weak initiators of carcinogenesis but are potent promoters of hepatic carcinomas. Effects *in vivo* often differ from those *in vitro*, with the latter suggesting a greater risk. Epidemiologic studies have not revealed clear evidence for carcinogenicity of PCBs in field exposure situations. Because of this, the USDA has developed tolerances for PCBs and actionable levels for PBBs in animal products and feeds (see Table).

Tolerance/Action Levels		
	PCB Tolerance Levels	**PBB Actionable Levels**
Animal feeds	0.2 ppm	0.05 ppm
Milk (fat)	1.5 ppm	0.30 ppm
Red meat (fat)	3.0 ppm	0.30 ppm

Eggs	0.3 ppm	0.05 ppm

- To prevent residues in livestock or their products it is estimated the total dietary concentration of PCBs or PBBs should be less than 10% of any regulatory guidelines.

Turpentine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
All species	Minutes	Hours to ddays; potentially lethal	

Synonyms - Gum spirits, spirits of turpentine, oil of turpentine

Uses

- Used as a treatment for bloat.
- It is a constituent of stimulating ointments.
- Industrially:
    - Insecticide.
    - Solvent for waxes, production of synthetic camphor.
    - In shoe, stove and furniture polish.
    - As a diluent for oil paints and to clean brushes.

Toxicity

- Adult (Human) - 140 ml orally may be fatal.
- Pediatrics (Human) - 15 ml turpentine-benzene mixture orally was fatal, but 2 - 3 ounces of turpentine have been ingested with survival.
- Turpentine is readily absorbed through the skin, gastrointestinal tract, and lungs.

Signs and Lesions

- General.
    - Depression.
    - Lethargy.
    - Nausea.
- Topical.
    - Can produce a severe rubefacient effect.
    - Warmth, redness of the skin.
    - Vocalization consistent with intense pain.
    - Vesicular eruption.
    - Urticaria.
- Ingested.
    - Burning abdominal pain.
    - Excitement, delirium, ataxia.
    - Convulsions, coma.
    - May cause nephritis.
- Inhaled (high concentration).
    - Hyperpnea.
    - Tachycardia.
    - Convulsions.
    - May cause nephritis.

Treatment

- Emesis is probably contraindicated.
- Activated charcoal and saline cathartic.
- Control seizures with diazepam (in appropriate species), or if it fails, give phenobarbital IV, if seizures still cannot be controlled induce anesthesia with pentobarbital.
- Dermal.
  - Rinse skin with copious amounts of water and wash with a mild liquid dish detergent.
  - If necessary, medicate skin to control drying, cracking, secondary self trauma, and infection.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Diesel Fuel (Petroleum hydrocarbons)	All species	Minutes to hours	Hours to days, rarely lethal	
Kerosene (Petroleum hydrocarbons)	All species	Minutes to hours	Hours to days, rarely lethal	
Other solvents	All species	Minutes to hours	Hours to days, rarely lethal	
Formaldehyde and Formalin	All species	Minutes to hours	Hours to days, rarely lethal with skin only exposure, toxicoses rare	
Phenolics	(See Toxicants that Affect the Liver)			
5-Fluorouracil (Effudex ®)	-	-	-	

- *Diesel fuel (See Organic Compounds that Affect the Lungs)
- Kerosene (See Organic Compounds that Affect the Lungs)
- Other Solvents (See Organic Compounds that Affect the Lungs)
- Phenolics (See Toxicants that Affect the Liver)
- Formaldehyde and Formalin

3. Other Plants that Affect the Skin (Integument)

Vicia villosa - Hairy Vetch

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Herbivores	Chronic	Months; often lethal	

Habitat

Hairy vetch (Roth Vetch, Winter Vetch), *Vicia villosa*, is a pasture plant that is high in protein and deliberately sowed in some areas. Has been reported to be a problem in Oklahoma, grows in Midwest also.

Toxic Principles

- In some types of vetch seed, cyanide is a potential problem.
- Hepatotoxins occur in others.
- The agent causing dermal lesions has not yet been characterized.

Signs

- Two primary syndromes occur in the bovine animal.
  - Delirium and rapid death syndrome.
  - Dermal, gastrointestinal syndrome.
    - Dermatitis.
    - Conjunctivitis.
    - Anorexia.
    - Weight loss.
    - Increased temperature.
    - Diarrhea, often bloody.
- The dermatitis associated with hairy vetch is associated with pruritus. Lesions begin with alopecia of the udder, tailhead, neck and later affect the face, trunk and the limbs. It is notable that black animals are most affected and especially those over 3 years of age.
- The onset is after 2 - 3 weeks of grazing and a low morbidity of approximately 6 - 8% is seen. In animals affected, however, the mortality may be high, up to 50% in some cases. Death occurs 10 - 14 days after the onset in most cases.
- The syndrome occurs especially in the late spring when the plant is growing maximally, and less often late in the season, although toxicosis may also occur from consumption of vetch in hay.
- The dermal, gastrointestinal (granulomatous) syndrome has also been recognized in horses.

Lesions

- In addition to dermatitis in the skin, lesions seen histologically may include macrophage, lymphocyte and plasma cell as well as giant cell and eosinophil infiltration into the heart, adrenal gland, kidney, thyroid, brain, and lungs.
- Grossly these areas of infiltration may be identifiable as gray or gray-yellow foci or streaks in the above mentioned tissues. Lymph nodes may be normal in size to markedly enlarged.

Winter Vetch (*Vicia villosa Roth*)

Family - Pea (Leguminosae)
Growth Form - Annual herbs.
Stems - Stems spreading to ascending, hairy, up to 2 feet long.
Leaves - Alternate, divided into 16 - 24 leaflets, the leaflets usually narrowly oblong, pointed at the tip, tapering or rounded at the base, without teeth, smooth, up to 3/4 inch long.
Flower Arrangement - Flowers several, in 1-sided axillary racemes, the racemes up to 4 inches long.
Flowers - Violet and white, up to 1/2 inch long, borne on very short stalks.
Sepals - 5, green, hairy, united below.
Petals - 5, violet and white, arranged to form a pea-shaped flower.
Stamens - 10.
Pistils - Ovary superior.
Fruits - Pod oblong, up to 1 1/4 inches long, smooth or nearly so.
Habitat - Fields and along roads.
Range - Throughout the state.
Time of Flowering - June to August.
Associated Plants - Hairy chess (*Bromus tectorum*), horseweed (*Erigeron canadensis*), white sweet clover (*Melilotus alba*), and common evening primrose (*Oenothera biennis*).

Hippomane Mancinella - Manchineel Tree

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Skin Effects other than Photosensitization
Most species	Minutes to hours	Days, rarely lethal	

Description

The manchineel tree (*Hippomane mancinella*) is 10 - 20 feet tall with a small trunk up to 6 inches in diameter.

Habitat

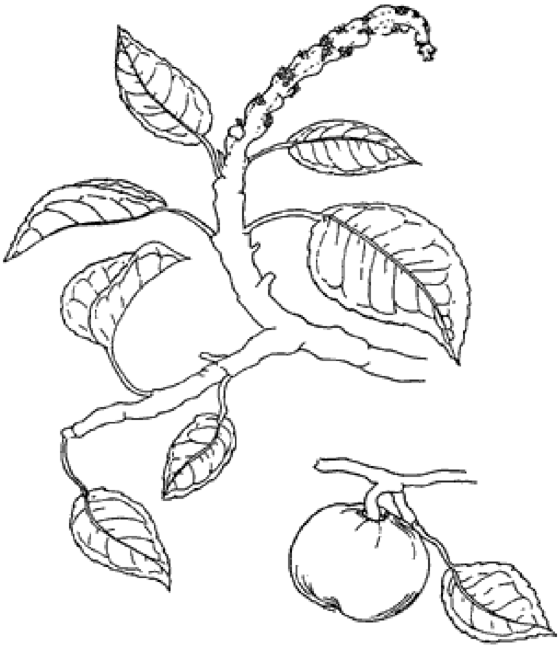
In the USA, the tree is restricted to Florida, south of Palm Beach and Fort Meyers. The tree is now primarily found in the Everglades.

Toxic Principle

- One reason for the restricted range of this tree is that the early settlers destroyed the tree wherever they found it, because of its extremely caustic resin.
- The fruit, which is not bad tasting, is also toxic.

Signs

- Plant (resin) contact effects:
    - Severe skin or eye irritation.
- Fruit ingestion, effects:
    - Vomition.
    - Abdominal pain.
    - Bloody feces.
    - Occasional deaths.



Manchineel tree (*Hippomane mancinella*)

Section XII: Toxicants that Affect the Gastrointestinal Tract

Forms of Energy, Chemicals and Drugs that Affect the Digestive Tract

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1. Radiation

Radiation Toxicology

Ionizing Radiation

- Definitions:
  - Ionization - removal or addition of electrons.
  - Direct ionization - ionization due to the mass and motion of a charged particle which imparts an electrical force to electrons in orbit.
  - Indirect ionization - ionization attributable to collision of an atom with a particle bearing no charge but which thereby liberates ionized (charged) particles.
- Types of electromagnetic radiation.
  - Gamma rays and x-rays - short wavelength; high frequency, good penetration.
    - Gamma (γ) rays originate from unstable atomic nuclei which release energy to gain stability. Ionization occurs primarily via indirect ionization.
    - X-rays originate outside of the nucleus of atoms, and ionization occurs primarily via indirect ionization.
- Types of particulate radiation (subatomic particles of varying masses and charges).
  - Alpha (α) particle: Two neutrons and 2 protons; arise from decay of heavy metals such as U, Pl, Ra, Th. Have high mass and 2 positive charges which results in large direct ionization potential but very little penetration.
  - Beta (β) particle = β-: An electron which arises from conversion of a neutron to a proton in the nucleus. Have high penetration but low ionizing power as compared to an alpha particle.
  - Positron particle = β+: Like a beta particle but positively charged. Same mass; arises when a proton is converted to a neutron.
  - Neutron: An electron combined with a proton which therefore has no charge and can only cause indirect ionization. Readily penetrates; free neutrons undergo β decay.
  - Proton: A hydrogen ion; potent ionizer, produced by neutron interactions.

Radioactive Decay

- Radioactive decay is decay of unstable isotopes by the emission of subatomic particles and gamma or x-rays.
- Heavy elements generally decay by emission of alpha particles.
- Lighter elements generally decay by beta emission.
- T 1/2 =

$$\frac{0.693}{\text{lambda}}$$

where lambda = the radioactive decay constant.

Units of Radioactivity

- Curie = Ci = 3.7 x 10^{10} nuclear disintegrations per second.
- Roentgen = R = a measurement of the quantity of ionizations induced in air.
  - 1R = 2.58 x 10^{-4} coulomb/kg of air.
  - 1R = 0.0096 joules/kg of tissue for gamma radiation.
- Rad = A unit used to express doses of radiation absorbed by living matter.
  - 1 Rad = 100 ergs/g tissue or

    - 1 Rad = 0.01 J/kg of any medium.
- Gray (of gamma radiation) = 1J/kg = 100 rads or 100 rems.
- Rem = Amount of any radiation that produces a biological effect equivalent to that resulting from 1 rad or 0.01 gray of gamma radiation.
- Seivert = Amount of any radiation that is equivalent in biological effect to 1 gray of gamma radiation.
    - 1 Seivert = 100 rems or 100 rads.
- For a given dose of differing types of radiation as measured in roentgens, rads, or grays, there is wide variation in effects. Usually particulate radiation is more injurious than electromagnetic.
- Quality of radiation is sometimes described in terms of linear energy transfer = LET.
    - LET = rate of energy transfer = a function of energy and velocity.
    - Higher LET = means greater injury for a given absorbed dose.

Radiation	LET
Protons, alpha particles	High
X-rays, gamma rays	Low

Sources of Ionizing Radiation

- Natural Background Radiation:
    - Cosmic rays.
    - Disintegration of radioactive elements in earth's crust.
    - Emission from naturally occurring isotopes in the body.
- Average background exposure - human - is: 80 millirems/year = 0.8 milliseiverts/year at sea level.
    - In mountains exposure is 2 times as high due to cosmic rays which are 3 times as intense.
    - In areas where radium or other isotopes are in abundance exposure increases.
- Man-made Exposure - Human:
    - Medical diagnostic - average = 70 millirems/year
    - Nuclear power - average = 0.003 millirems/year
    - Global fallout - average = 4.0 millirems/year
    - Radiopharmaceuticals - average = 1.0 millirems/year
    - **Subtotal 75 millirems/year**
    - Occupational and miscellaneous = 2 - 8 millirems/year
    - e.g.: Industrial, television, air travel.
    - **Total average human exposure = 150 - 180 millirems/year**

Two Effects of Ionizing Radiation

- **Ionization**, e.g. orbital electron is ejected which results in the formation of an ion pair.
    - Example: ionization of water.
      $HOH \rightarrow HOH^{+} + e-$
      $HOH^{+} \rightarrow H^{+} + OH$
      ion pair
- Excitation
    - An electron is raised to a higher energy state.
    - Molecule may be excited with energy exceeding that required for ionization and may lose energy by dissociation into free radicals (i.e., H. and OH.) without passing through the stage of ionization.
    - In biological systems the free radicals H. or OH. exist for only a fraction of a second and react to form H_2O, H_2, or hydrogen peroxide or may react with macromolecules such as DNA. The most fundamental effect of ionizing radiation on biological systems is the ionization of water with the formation of free radicals, $H_{\cdot}$ and $OH_{\cdot}$.

Note: There are 5 classes of cells with regard to radiosensitivity.

- In decreasing order of sensitivity these are:
    - Vegetative intermitotic cells (most sensitive).
        - Hematopoietic stem cells.
        - Intestinal gland cells.
        - Spermatogonia type A cells.

        - Ovarian granulosa cells.
        - Large and intermediate lymphocytes.
        - Germinal cells of the epidermis.
        - Gastric and holocrine glands.
    - Differentiating intermitotic cells.
        - Hematopoietic cells in differentiation.
        - Differentiated spermatogonia, spermatocytes, oocytes.
    - Multipotential connective tissue cells.
        - Endothelial cells.
        - Fibroblasts.
        - Mesenchymal cells.
    - Reverting postmitotic cells.
        - Epithelial parenchymal cells.
        - Salivary gland duct cells.
        - Liver.
        - Kidney.
        - Pancreas.
    - Fixed postmitotic cells.
        - Neurons.
        - Muscle.
        - Neutrophils.
        - Erythrocytes.
        - Spermatids.
    - Extrinsic and intrinsic factors influence the response of a living organism to a given dose of radiation.
    - Extrinsic factors:
        - Dose quality of radiation.
        - Part of body exposed.
    - Intrinsic factors:
        - Species.
        - Sex.
        - Age.

Effects of Radiation Toxicosis

- Early to Intermediate Effects:
    - At greater than 50 rads radiation sickness occurs as does pulmonary fibrosis.
    - A sensitive indicator of irradiation is the frequency of chromosomal aberrations in lymphocytes. This measurement is useful when the whole body or a major part is exposed to 25 rads or more.
    - Cell death causes most early effects of radiation toxicosis.
    - The rate of mitosis is generally related to radiosensitivity.

Clinical Signs and Effects of Acute Whole Body Exposure to Radiation

- Clinical manifestations most commonly involve 4 forms.
    - Hematopoietic and immune.
    - GI.
    - Skin
    - Reproductive
- Manifestation of early effects occur only after doses of greater than 50 rads, and this must be at a relatively high rate of dosing such as several rads per hour.
- At 50 - 1000 rads:
    - Bone marrow is damaged.
    - The first decrease seen is in lymphocytes and this occurs in 1 - 2 days.
    - There is an early increase in PMNs which may be followed by a leveling off; this is termed an "abortive rise". **Failure** to see the abortive rise is a bad sign and results in a poorer prognosis.
    - PMNs may decrease in numbers for 4 - 6 weeks then increase slowly to normal within a few months.
    - Platelet sensitivity is similar to that of PMNs. Hemorrhage occurs if platelet counts fall too low.

Signs	Estimated Dose Required
Anorexia	120 rads
Nausea	170 rads
Vomiting	210 rads
Diarrhea	240 rads
Apathy	
Tachycardia	
Fever	
Headache	

  - At very high doses of greater than or equal to 1000 rads, the prodromal response merges with a fatal gastrointestinal syndrome.
  - One-thousand to 5000 rads results in a 5 - 10 day survival, death attributable to uncontrollable bloody diarrhea.
  - At over 5000 rads death due to neurologic and cardiovascular degeneration occurs in minutes to 48 hours.

- Whole Body Exposure - Acute LD_{50} for Irradiation of Various Species:

Animal	Rads
Mouse	638
Rabbit	751
Dog	244
Pig	247
Sheep	205
Goat	237
Monkey	546
Burro	246

  - The 60-day estimated LD_{50} for man is estimated to be 300 rads.
  - Survival is probable at 100 - 200 rads and possible at 200 - 500 rads but not possible at over 500 rads.

Partial Body Exposure to Radiation

- Usually results in atrophy and fibrosis of some organs and late focal necrosis in others.
  - With partial body exposure to irradiation at doses of:
    - 10 - 100 rads: there may be a decrease in sperm count.
    - 500 rads: redness of skin; permanent sterility.
    - Less than 500 - 1000 rads: serious effects are usually not immediately evident except in skin, eyes, and gonads.

Late Effects of Low Level Exposure to Radiation

- Carcinogenesis
  - Increase in leukemia occurred in areas of Japan hit by atomic bombs.
- Mutagenesis and chromosomal aberrations.
  - Somatic and germinal cells.
  - Point or gene mutations.
  - Deletions.
  - Duplication.
  - Inversion.
  - Translocation.

2. Metals, Other Elements, and Inorganic Compounds that Affect the GI Tract

Arsenic and Antimony

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
Arsenic (Many sources, including ashes from CCA [wood-preservative]-treated lumber)	All species	Hours to chronic	1 - 7 days; often lethal	Full Table for Forms of Energy, Chemicals and Drugs that Affect the Digestive Tract
Antimony	All species	Hours to chronic	1 - 7 days; often lethal; toxicosis is rare	

- Inorganic, aliphatic, and trivalent organic arsenicals are discussed in this section.
- Phenylarsonics such as arsanilic acid; and the trivalent phenyl arsenical, thiacetarsemide (Caparsolate ®) are discussed in **other** sections of these notes.

Sources

- Background (natural) sources include pyrites (FeS_2. $FeAs_2$) and sulfides (As_2S_2,3).
- Heating to refine metal ores results in the production of arsenic trioxide (As_2O_3) some of which is carried to the surrounding countryside in dust or smoke.
- Herbicides or defoliants - arsenic trioxide, sodium arsenite or arsenates of sodium, potassium, calcium or lead, monosodium methanearsonate (MSMA) or disodium methanearsonate (DSMA), grass clippings contaminated by herbicides.
- Insecticides - Paris green (copper acetoarsenite), arsenic trioxide, lead arsenate. Dipping vats containing arsenic trioxide.
- Some vermiculite, Celotex sheathing.
- Insulation, ant baits, rodent baits, inorganic arsenic contaminated soil and forage are all consumed by animals.
- Paint pigments - emerald green.
- Outmoded medications - Fowler's solution, arsphenamine, acetarsol, sodium cacodylate.
- Arsenic treated wood products, and **much more likely**, ashes from copper, chromium, and arsenic (CCA) treated wood.
- Burn piles from any of many sources of arsenic.
- Litter from poultry fed phenylarsonic compounds can contain considerable arsenic.
- Arsine is the hydride gas (ASH_3) of arsenic which is an industrial gas or a gaseous product of the charging of storage batteries. It causes hemolysis.
- **Note**: Antimony exerts toxic effects similar to arsenic. Stibine, antimony hydride, like arsine is a gas which may induce hemolysis.

Susceptible Species

- All species susceptible.
- Poisoning most common in bovine and feline animals.
- Next most common in horses and sheep.
- Occasional poisoning of dogs.
- Rare in swine, poultry.
- Animals weak, debilitated and dehydrated are much more susceptible to arsenic, perhaps due to reduced renal excretion.

Toxicity

- Trivalent arsenicals are more toxic than pentavalent.
  - Trivalents include arsenic trioxide; salts of arsenious acids (H_3AsO_3) which are called arsenites.

  - Lethal oral dose of sodium arsenite for most species is from 1 - 25 mg/kg with arsenic trioxide being 3 - 10 times **less** toxic.
  - LD_{50} rat oral: sodium arsenite - 42 mg/kg; arsenic trioxide - 385 mg/kg.
  - Pentavalents include arsenic pentoxide, salts of arsenic acid (H_3AsO_4) which are called arsenates, and other compounds, such as cacodylic acid, trimethylarsine oxide, MSMA and DSMA.
  - Cats are highly sensitive to arsenicals and may succumb to sodium arsenate (in Old Terro Ant Poison) at a dose of 20 mg/kg.
  - In drinking water of swine the lethal dose of sodium arsenite was 100 - 200 mg/kg BW.
- Toxicity is also influenced by:
  - Solubility of formulation (arsenic trioxide less soluble than sodium arsenite).
  - Route of exposure.
  - Rate of absorption.
  - Rate of metabolism and excretion.
  - Acceptability to animals.
- Cattle died after 5 daily doses of MSMA at 10 mg/kg BW, and 6 daily doses of DSMA at 25 mg/kg. After ten daily doses of MSMA at 5 mg/kg and DSMA at 10 mg/kg no ill effects were observed.
- Sheep died after 6 daily doses of MSMA at 50 mg/kg and 6 daily doses of DMSA at 25 mg/kg. Sheep given 10 daily doses of MSMA at 25 mg/kg and DSMA at 10 mg/kg exhibited no ill effects.
- Chickens tolerated 10 daily, 250 mg/kg doses of either compound.
- MSMA is recommended at 2 lb per acre, and DSMA at 3 lb/acre. Therefore, if applied at the recommended rate, MSMA would be hazardous for cattle but not sheep or chickens; DSMA would be hazardous for cattle and sheep but not chickens.
- Eight to 10 daily doses of cacodylic acid at 25 mg/kg BW were toxic to cattle or sheep.
- Ten daily doses of cacodylic acid at 100 mg/kg caused only reduced weight gains in chickens.
- Cacodylic acid is recommended at 8 lb per acre, therefore fields treated with cacodylic acid are likely to pose a hazard to cattle and sheep but not poultry.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Soluble forms of arsenic such as sodium arsenite are readily absorbed from all body surfaces.
- Less soluble forms are poorly absorbed from the digestive tract and are excreted largely unchanged in the feces.
- Once absorbed:
  - Pentavalent arsenicals are readily excreted in the feces.
  - A fraction of the absorbed portion of pentavalent arsenic is reduced to the trivalent form in the kidneys; this conversion may account for nephrotoxicity.
  - Trivalent arsenicals are more readily excreted into the intestine via the bile.
  - Methylation of arsenic is an important detoxification mechanism and significant excretion of methylated arsenic compounds occurs.
- Many texts indicate that arsenic generally accumulates in tissues and is only slowly excreted. While true for the rat, domestic animals are able to eliminate considerable arsenic over a period of days.

Mechanism of Action

- Regardless of the form entering the body (pentavalent or trivalent), the major effects are believed to be attributable to the trivalent form.
- Primary effects of trivalent arsenic are believed to be due to their reaction with lipoic acid to form a stable compound that subsequently disrupts enzymes involved in cellular respiration.
- Arsenic affects those tissues rich in oxidative enzymes, especially the alimentary tract, kidney, liver, lung and epidermis. Arsenic is a potent capillary poison and although all beds are affected, the splanchnic area is most sensitive. Loss of capillary integrity and dilation allows transudation of plasma fluids into the intestinal mucosa and lumen which results in sharply reduced blood volume, hypotension, shock and circulatory collapse. Edema, vesiculation and eventual loss of the gastrointestinal mucosa may occur as a result of the transudation of fluid and capillary damage. This further aggravates fluid losses and shock.
- Toxic arsenic nephrosis is common in small animals and man. Glomerular capillaries dilate, swell and varying degrees of degeneration occur. The hypotension and dehydration contribute to oliguria and the urine contains red blood cells and casts.
- Following percutaneous absorption, capillary dilation and degeneration cause blistering and edema. Skin becomes dry, papery and may crack, bleed and develop secondary infections.

- The arsenate (pentavalent) ion may uncouple oxidative phosphorylation. Rather than the typical febrile response that occurs with other uncouplers, this effect of arsenic has been associated with peripheral nerve or spinal cord dysfunction in man.
- The hydride gas of arsenic, arsine, combines with hemoglobin and is oxidized to a hemolytic metabolite that does not apparently depend on sulfhydryl inhibition.

Signs

- Acute and peracute toxicosis.
    - Common to have peracute and acute episodes of inorganic arsenic poisoning with high morbidity and mortality over 2 - 3 days.
    - Intense abdominal pain.
    - Staggering, extreme weakness, trembling.
    - Salivation, vomiting (in dogs, cats, pigs and perhaps even cattle).
    - Diarrhea.
    - Fast, weak pulse.
    - Prostration, rumen atony.
    - Hypotension, dehydration, oliguria.
    - Normal or subnormal temperature.
    - Death.
    - Severity of clinical signs in cattle correlates with hemoconcentration as indicated by the PCV.
- Subacute toxicosis.
    - May live for several days.
    - Depression, anorexia.
    - Watery diarrhea, may contain shreds of intestinal mucosa.
    - Polyuria then anuria.
    - Dehydration, polydipsia.
    - Weakness or partial paralysis of the rear limbs.
    - Trembling, stupor, cold extremities, hypothermia, death.
    - Convulsions rarely occur.
- Chronic toxicosis.
    - Rarely seen in domestic animals, well documented in man.
    - General loss of condition, rough hair coat.
    - Brick red discoloration of the visible mucous membranes.
- In man the trivalent organic arsenicals may cause circulatory, gastrointestinal, renal and dermal effects much like the inorganic arsenicals. In addition, affected people may also experience nerve damage with effects similar to those of the phenylarsonic acid feed additives (similar to those of arsenilic acid, in swine and poultry).
- Following percutaneous absorption, capillary dilation and degeneration cause blistering and edema. Skin becomes dry, papery and may crack, bleed and develop secondary infections.

Lesions and Clinical Pathology

- On occasion, in peracute toxicosis, no lesions may be seen.
- More often characteristic lesions occur and include:
    - Redness of gastric or abomasal mucosa (localized or generalized).
    - Redness of small intestinal mucosa; most often the first few feet of the duodenum.
    - Fluid gastrointestinal contents which are often foul smelling and may contain blood.
    - Soft yellow liver (sometimes).
    - Red edematous lungs (sometimes).
    - Redness of the gastrointestinal mucosa is followed by edema, rupture of blood vessels and necrosis of the mucosa and submucosa.
    - Infrequently the necrosis progresses to perforation of either the intestine or stomach.
    - Occasionally hemorrhages may occur on all surfaces of the heart.
    - Histologic changes include mucosal and submucosal edema and necrosis and sloughing of the mucosa in the gastrointestinal tract.
    - Acute renal damage affects all portions of the nephron with glomerular sclerosis and severe renal tubular necrosis. Toxic arsenic nephrosis is common in small animals and man. Glomerular capillaries dilate, swell and varying degrees of degeneration occur. The hypotension and dehydration contribute to oliguria and the urine contains protein, red blood cells and casts.

    - Hepatic fatty degeneration and necrosis.
    - Cutaneous exposure - dry, leathery, peeling skin.

Diagnosis

- Rapid onset of gastroenteritis, excess fluid in the gastrointestinal tract.
- Weakness, prostration.
- Rapid death.
- Redness, edema and necrosis of gastrointestinal mucosa.
- Liver, kidney, stomach and intestinal contents and urine should be analyzed for arsenic.
- Renal tissue and often liver will contain 8 ppm or more arsenic.
- By several days after exposure, however, the liver and kidney may contain only 2 - 4 ppm arsenic.
- Gastrointestinal tract contents and urine may contain from 2 - 100 ppm arsenic and may aid in assessment of the route and degree of exposure.
- Differential diagnosis, see *Clinical and Diagnostic Veterinary Toxicology*.

Treatment

- Prognosis is often poor, especially if not diagnosed and treated promptly.
- Emesis and vigorous lavage may possibly be contraindicated after severe clinical signs have developed, due to the possibility of increasing the likelihood of perforation and shock.
- For very recent exposure, however, emetics are indicated in capable species provided that contraindications are not present.
- Activated charcoal is indicated in recent oral exposure.
- Lavage or enterogastric lavage may also be indicated.
- Saline cathartics are usually not indicated once diarrhea has begun. However, oral administration of sodium thiosulfate may be of value to bind arsenic. Sodium thiosulfate has not, however, been clearly demonstrated to be of benefit. The dose of sodium thiosulfate for arsenic toxicosis is 30 - 40 mg IV or orally as a 10 - 20% solution and in one study of calves was of no apparent value.
- Vigorous fluid and electrolyte therapy are indicated.
- B complex vitamins are indicated in the fluids.
- Renal function should be monitored and urinary flow may be promoted using 10% dextrose solution. If catheterization of the urinary bladder reveals increased urinary flow and glycosuria, fluids should be continued. Preferably, lactated Ringer's solution should be alternated with 5 or 10% dextrose. If acidosis is present, sodium bicarbonate should be added to the fluids.
- If hypotension and/or renal output are not responsive to fluid therapy, dopamine administration may be needed.
- Whole blood should be administered as indicated in animals with gastrointestinal hemorrhage.
- Kaopectate may be used to sooth the damaged mucosa.
- A high protein, low residue diet is recommended during the postexposure period.
- Chelating agents for arsenic include:
    - British antilewisite (BAL or dimercaprol). BAL is prepared as a 5% mixture in a 10% solution of benzyl benzoate in arachis oil. BAL is of questionable value in large animals but may be of value in small animals when administered at 3 mg/kg BW IM or if signs are already present at 6 - 7 mg/kg BW IM. Doses (3 mg/kg) are repeated 3 times a day until recovery. Renal function should be monitored during therapy.
    - Side effects of BAL exposure are dose dependent and may include tachycardia, anorexia, vomiting, hypersalivation, fever, and seizures. Also, injection sites tend to become painful.
    - Mesodimercaptosuccinic acid (DMSA) (Succimer®) is probably the preferred chelator at this time. It is much safer than BAL. It may confer a sulfur odor to the breath and urine.
    - 2,3-dimercapto-1-propanesulfonic acid, sodium salt (DMPS).
    - N-acetylcysteine (Mucomyst®) increased the LD_{50} (decreased the toxicity) of sodium arsenite in experimental mice although little data on its clinical use in arsenic toxicosis is available. It has the advantage of being the only chelator which can be given IV for acute arsenic toxicosis.
- Thioctic acid (Sigma Chemical Co., St. Louis, MO) was found to be superior to BAL in arsenic exposed calves. Thioctic acid may also be used in combination with BAL. The product DL-6,8-thioctic acid (Sigma Chemical Co., St. Louis, MO) is administered as a 20% solution. This is made up by adding 50 grams to 100 ml of warm SN NaOH, then cooled and adjusted to pH 6.8-7.0 with IN NCl, and then made up to volume with distilled water. It is then dosed at the rate of 50 mg/kg BW given IM at 2-3 injection sites every 8 hours.

- Mesodimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid, sodium salt (DMPS) are water soluble analogues of dimercaprol (BAL). As compared to BAL these agents have less toxicity, greater water solubility and are effective when given orally.
    - DMSA (Succimer®) but not DMPS is available in the USA. Reference DMSA and DMPS: Ann. Rev. Pharmacol. Toxicol. 23:193-215.
    - DMSA and DMPS have been used extensively in the USSR, the People's Republic of China and Japan. DMSA was originally used to control toxicosis due to the therapeutic use of antimony in schistosomiasis. DMPS is known as Unithiol in the USSR. DMPS is also available from Heyland Co., Berlin.
    - DMSA was effective in man at a total dose of 300 mg, every 6 hours, PO for 3 days.
    - DMPS was effective when given to arsenic exposed rabbits at 30 mg/kg subcutaneously. DMPS prevented the lethal effects of many arsenic compounds. DMPS is used in man in the USSR at 5 mg/kg.
    - These agents are probably superior to most, if not all other, presently used chelation agents employed for lead, mercury and other heavy metal toxicoses in the USA. Both DMPS and DMSA are known for their low toxicity. Both are less toxic than BAL.
    - At 100 mg/kg the effectiveness of DMPS is increased, but necrotization and ulcerations often occur at the site of the subcutaneous or IV injection.
    - The same lesions occurred when pigs were given 0.20 mmol DMPS/kg IM or SC, but no such necrosis occurred with DMSA.
    - When dogs were given DMPS at 50 mg/kg IV, some of them exhibited muscle tremors, tachycardia, dyspnea, vomiting and defecation. Lethargy and cramps were sometimes observed.
    - Cats are more sensitive to adverse effects of DMPS than dogs.
    - The t-1/2 for DMPS in dogs is 43 minutes.
    - As an arsenic antidote for mice, the therapeutic index of DMSA is 3 times greater than that for DMPS. DMPS, in turn, is 28 times better than BAL in this respect.
    - DMSA is also more effective than DMPS in removing mercury from the body, thus DMSA is probably preferable even when compared to DMPS.
    - In human beings, chelation is continued until the 24-hour urine collection yields an arsenic concentration less than 50 micrograms/L.
      Note - Seafood ingestion may increase urine arsenic well above this level and therefore seafood products must be avoided for the test to give a meaningful result.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Forms of Energy, Chemicals and Drugs that Affect the Digestive Tract
Chromates	All species	Hours to chronic	Days; potentially lethal	
Fertilizer	All species	Up to 24 hours	1 - 3 days; rarely lethal in small animals; potentially lethal in ruminants	
Molybdenum	Ruminants	Chronic	Days to weeks, potentially lethal	
Elemental and Inorganic Salts of Mercury (acute)	See Toxicants with Mixed Effects on the CNS			
Lead (Acute)	See Toxicants with Mixed Effects on the CNS			
Thallium (Acute)	See Toxicants that Cause Skin Effects Other Than Photosensitization			
Cadmium (Acute)	See Toxicants that Affect the Kidneys			
Copper (Acute)	See Toxicants that Cause Hemolysis			

Phosphorus (Initial)	See Toxicants that Affect the Liver	
Zinc Phosphide (Initial)	See Toxicants Associated with Stimulation or Seizures	
Zinc (Acute)	See Toxicants that Affect the Kidneys	

- Chromates
- Elemental and Inorganic Salts of Mercury (See Toxicants with Mixed Effects on the CNS)
- Lead (Initial) (See Toxicants with Mixed Effects on the CNS)
- Thallium (Acute) (See Toxicants that Cause Skin Effects Other Than Photosensitization)
- Cadmium (Acute) (See Toxicants that Affect the Kidneys)
- Copper (Acute) (See Toxicants that Cause Hemolysis)
- Phosphorus (Initial) (See Toxicants that Affect the Liver)
- Zinc (See Toxicants that Affect the Kidneys)
- Zinc Phosphide (Initial) (See Toxicants Associated with Stimulation or Seizures)
- Fertilizer

3. Organic Compounds that Affect the GI Tract

Nonsteroidal Anti-Inflammatory Agents

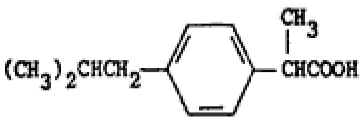
See also Analgesic Nephropathy

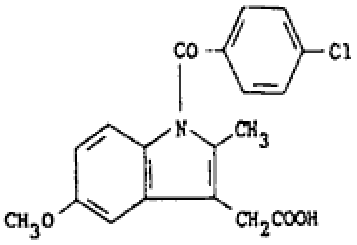
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Forms of Energy, Chemicals and Drugs that Affect the Digestive Tract
Most species	Hours to days	Days to weeks; often lethal	

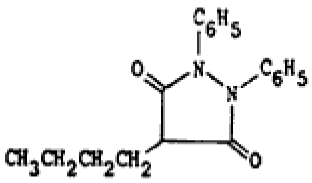
Sources

- Human and veterinary drugs. In recent years, major problems from prescription medicines including ibuprofen (Motrin®), and especially in over-the-counter products such as ibuprofen (Advil ®) and naproxen (Naprosyn ®).

Structures







Ibuprofen

Indomethacin

Phenylbutazone

Toxicity

- Generally, toxicosis is a result of large overdoses, although the cat is predisposed to toxicosis, especially in the case of acetaminophen and aspirin, both of which are discussed elsewhere in this course.

- Principal effects are on the digestive system, the central nervous system and the kidneys.
- Clinical reports indicate that doses of approximately 100 mg of ibuprofen/kg BW can cause serious toxicoses in dogs. Approximately 50 mg of ibuprofen/kg/BW can cause serious toxicoses in cats.
- Phenylbutazone has been associated with renal papillary necrosis at typical doses (8.8 mg/kg) especially if animals are dehydrated or have received multiple dosages of phenylbutazone.
- Flurbiprofen (Ansaid) may cause severe gastric damage at a dose of 1 mg/kg and an ulcerogenic effect may be noted at 0.04 to 0.2 mg/kg.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Many of the NSAIDs are highly protein bound which may predispose to drug interactions.
- Ibuprofen is 90 - 99% protein bound (man), therefore, the concurrent use of drugs which are protein bound in animals already carrying excessive ibuprofen on the albumen (overexposed animals) may aggravate the likelihood and severity of toxicosis. It is metabolized to inactive metabolites and excreted in the urine largely as metabolites or glucuronide.
- Indomethacin is 90% protein bound (man).
- Peak plasma concentrations of indomethacin in man at therapeutic doses are reached at 1 - 4 hours.

Mechanism of Action

- Known to interfere with prostaglandin synthesis via cyclooxygenase inhibition. In view of the known modulating effects of prostaglandins on the microcirculation, it has been **suggested** that the NSAIDs may work by interference with circulation, which secondarily results in the gastrointestinal damage sometimes seen.
- Mechanisms by which NSAIDs can effect renal function may include: **1**) decreased synthesis of renal vasodilatory prostaglandins (PGE_2 and PGI_2 prostacyclin), **2**) allergic interstitial nephritis, **3**) impaired renin secretion, and **4**) enhanced tubular water and sodium reabsorption (see section on Analgesic Nephropathy).
- Generally NSAID have little effect on GFR or renal blood flow in normal unstressed animals.
- Human dehydration and diuretic treatment predispose to NSAID induced acute renal failure. Patients with congestive heart failure, renal insufficiency, cirrhosis, SLE are also predisposed.
- Phenylbutazone also stimulates the respiratory center and like phenol and aspirin, an initial respiratory alkalosis may occur.

Signs

- Evidence of nausea, vomiting, and abdominal pain are the most common signs seen.
- Lethargy and drowsiness are next in frequency, ataxia and stupor may follow.
- A metabolic acidosis may occur and this would be expected to be followed by vomiting, and tachypnea, as well as weakness and possibly shock.
- Coma sometimes may occur as may (rarely) seizures.
- Transient apnea has been reported in human infants on occasion.
- It is possible to get esophageal strictures from the localization of tablets or capsules in the esophagus when they fail to reach the stomach.
- Acute renal failure occurs in some cases and may sometimes become the primary problem. Analgesic nephropathies have been reported in man receiving aspirin, phenacetin, indomethacin, and phenylbutazone. In dogs, ibuprofen is currently an important cause of nephropathies and gastric damage. NSAID-induced renal failure is characterized by an abrupt onset of oliguria. Some affected animals may show papillary necrosis and uremia.
- An increase in bleeding time may be seen.
- Phenylbutazone causes more hepatic and renal failure than most of the NSAIDs.

Lesions

- Gastrointestinal irritation and possible ulceration with associated hemorrhage and possible perforation.
- Renal tubular or papillary necrosis in a limited number of cases in dog. Phenylbutazone toxicity in dehydrated horses resulting in papillary necrosis is not uncommon.
- Rare esophageal damage if lodged in esophagus.

Treatment

- Early presentation: emetic if not contraindicated.
- Activated charcoal and a saline or osmotic (sorbitol) cathartic.
- Antacids.
- Maintain respiration if apnea or respiratory depression occurs.
- Dilution with large amounts of oral fluids may enhance absorption and should not be used without activated charcoal except to prevent medication from remaining in the esophagus.
- Therapy includes parenteral (iv) fluids, sucralfate (Carafate ®) if gastric ulceration is at all likely, and an H2-antihistamine (such as cimetidine [Tagamet ®]) at 5 - 10 mg/kg every 6 to 12 hours.
- Misoprostol (a prostaglandin E_1 analog) has recently been shown to be of considerable value in prevention of aspirin and other NSAID-induced gastric ulcers.
- If hypotensive, use fluids and, if blood pressure and urinary output are still not responsive, consider the use of dopamine HCl.
- If acidotic, fluids should contain bicarbonate (slow administration); this should be continued until the urinary pH ranges from 7 - 8; and maintained as needed to stabilize the urine pH in this range. Alkalinizing the urine is recommended by the manufacturer to promote the elimination of ibuprofen, but, because of the high percentage of protein binding, alkalinization of the urine of ibuprofen-poisoned people is not recommended by some authors.
- Dialysis does not enhance the elimination of ibuprofen.
- Phenylbutazone clearance has been shown to be enhanced by alkaline diuresis.
- When the specific NSAID is not known, alkaline diuresis may be tried in many instances in order to enhance excretion and may be of value even when the animal is not acidotic.
- Peritoneal dialysis may be indicated to offset the effects of severe renal failure.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Forms of Energy, Chemicals and Drugs that Affect the Digestive Tract
Cardioglycosides	See Toxicants that Affect the Heart			
Fluroacetate (1080) (Acute) (Esp. Canids)	See Toxicants that Cause Seizures			
Cholinesterase Inhibitors	See Toxicants that Affect the Autonomic Nervous System			
Rotenone	See Toxicants With Mixed Effects on the CNS			
Carbon Tetrachloride	See Toxicants that Affect the Liver			
Chlorophenoxy Herbicides	See Toxicants that Affect Primary Muscle Dysfunction and/or Paralysis			
Blister Beetles (*Epicauta*)	See Toxicants that Affect the Kidneys			
5-fluorouracil (Effudex ®) Topical Creme (When Ingested)	See Toxicants Associated with Seizures			
ANTU	See Toxicants that Affect the Respiratory System			
Scombroid fishes (deteriorated tuna, bonito, mackerel) (histidine → histamine)	-	-	-	
Dysautonomia Syndrome	-	-	-	

- Cardioglycosides (See Toxicants that Affect the Heart)
- Fluroacetate (Initial) (Canidae) (See Toxicants that Cause Seizures)
- Cholinesterase Inhibitors (See Toxicants that Affect the Autonomic Nervous System)
- Rotenone (See Toxicants With Mixed Effects on the CNS)

- Carbon Tetrachloride (See Toxicants that Affect the Liver)
- Chlorophenoxy Herbicides (See Toxicants that Affect Primary Muscle Dysfunction and/or Paralysis)
- Blister Beetles (*Epicauta*) (See Toxicants that Affect the Kidneys)
- 5-fluorouracil (Effudex ®) Topical Creme (When Ingested) (See Toxicants Associated with Seizures)
- ANTU (See Toxicants that Affect the Respiratory System)

Plants that Affect the Gastrointestinal Tract (Part I)

V. Beasley

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Proteins-Synthesis Inhibiting Lectins ("Toxalbulmins")

Abrus Precatorius (Crab's Eye, Precatory Bean, Rosary Pea, Jequirity Bean)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Horses, small animals	12 - 24 hours	Few days; often lethal	

Family - Leguminosae

Description

- Plant - Perennial vine, climbing on other plants, 10 - 20 feet tall.
- Stem - Woody, green when young, slender.
- Leaves - Alternate, opposite, pinnately divided, compound. Leaflets are small, oblong, in 8 - 15 pairs and 1/2 inch long.
- Flowers - Numerous inflorescences in leaf axils along stem. Racemes, 1 - 3 inch long. Flowers are many, small, red to purple or occasionally white.
- Fruit - Legume pod, 1.5 inches long, covered with fine hairs, contains many seeds, hard ovoid, 3/8 inches long. Seeds are bright, glossy, scarlet with jet black mark which covers 1/3 of the seed including the scar of attachment and the seeds are 0.2 - 0.3 inches long. The pod is somewhat septate between the seeds.

Habitat

Tropical locations such as Mexico and India. In the USA in central and southern Florida. Fence rows, citrus groves, occasionally cultivated as a screening vine or for the seeds which are made into rosaries and necklaces.

Toxic Principle

- The heat labile phytotoxin (a lectin, also termed a toxalbumin), abrin.
- The glycoside, baric acid.

Mechanism of Action

Protein synthesis inhibition by the toxalbumin.

Toxicity

- **General**:
    - Seeds are most toxic, seed coat retains the toxin, therefore if ingested whole, toxicosis is unlikely, toxicosis results from having chewed the seeds.
- **Human**:
    - Abrin is one of the most toxic compounds known and less than 1 masticated seed is sufficient to kill an adult human being.
    - Ingestion of 0.00015% of BW may be lethal.
    - Severe illness occurred after drinking tea in which 1 seed had soaked for 15 minutes.
    - Poisoning has occurred from a pricked finger while stringing the beans.

- **Horse**:
    - 14.8 ml (0.5 oz) of powdered seed produces clinical signs while 59 - 118 ml (2 - 4 oz) is lethal.
    - Humans and horses are more susceptible than are goats, cattle, and dogs.

Signs

- **General Signs**:

    - Oral and esophageal irritation, similar to caustic burns, seen by 2 hours.
    - Severe gastrointestinal irritation.
    - Nausea and vomiting, also dehydration.
    - Trembling, tachycardia.
    - Coma, hemolytic anemia, oliguria and sometimes uremia.
    - Incoordination to paralysis.
    - Circulatory collapse and death.
    - Nonfatal cases may proceed to secondary infections.

- **Humans:**

    - Hallucinations have occurred in children, in addition to the above signs.

- **Horses:**

    - Latent period.
    - Loss of appetite.
    - Violent purgation.
    - Elevation followed by depression in temperature.
    - Incoordination and sometimes paralysis.

- Toxicosis may be seen to occur in 2 general stages.

    1. Initial stage (2 - 24 hours after dosing), characterized by oral, esophageal and gastric irritation.
    2. Late stage (1 - 10 days), in which the following may occur:

    - Ocular hemorrhage (retinal and/or scleral).
    - Increased capillary permeability.
    - Hypotension and sometimes shock.

- CNS hemorrhage may also occur in some animals.
- Renal failure may be acute in some cases.

Lesions

- Inflammation and ulceration of the GI tract.
- Visceral hemorrhage and small thrombi formation.
- Multifocal necrosis in parenchymatous organs.
- Splenomegaly and multifocal necrosis in germinal centers of lymphatic organs.
- Possible hemolytic anemia and generalized petechial hemorrhage throughout the body.
- Possible hemagglutination.

Diagnosis

Identification of seeds of *Abrus precatorius*, evidence of consumption and appropriate clinical signs and lesions.

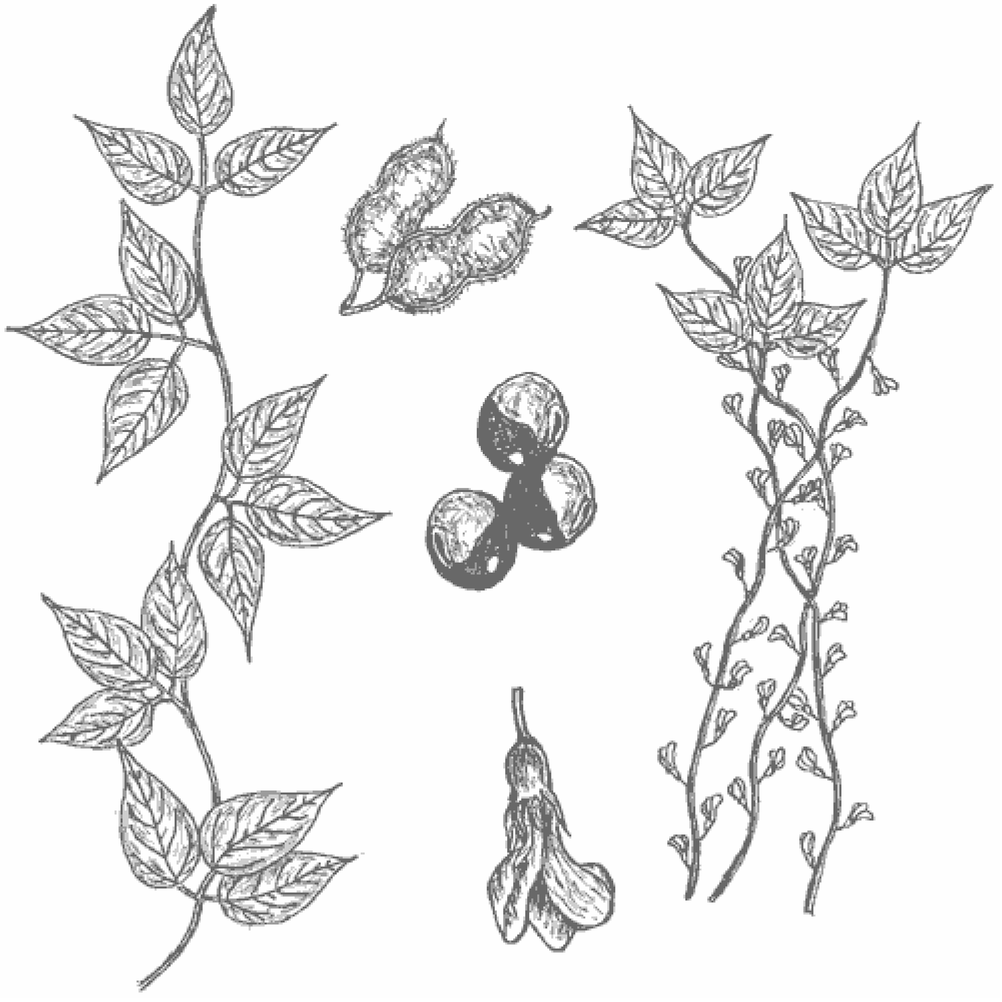
Treatment (Applies to Toxalbumins [Phytotoxins] in General)

- Induce emesis unless contraindicated by the condition of the animal.
- Maintain (or establish) respiration.
- Endotracheal intubation preceding gastric lavage.
- Activated charcoal with a saline cathartic, e.g., magnesium sulfate.
- Maintain fluid and electrolyte balance.
- Oral antacids to alleviate local irritation.
- Ascorbic acid increases survival rates.
- If there has been significant hemolysis, forced alkaline diuresis has been suggested to prevent nephrosis.
- If severe hemolytic anemia, consider exchange transfusion where possible.

Note - Drilled seeds as in necklaces are very toxic.

Prevention

Reportedly immunization via increasing doses is practiced in India.



Rosary Bean - The twining stem, the 3-foliate leaves, the legume flowers, the hairy seed pod, and the attractive red and black beans characterize this unusual plant.

Ricinus Communis (Castor Bean, Castor-Oil-Plant, *Palma Christi*)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Horses, dogs	12 - 36 hours	Few days; often lethal	

Family - Euphorbiaceae (spurge family)

Description

- *R. communis*:
    - Plant - Large, glabrous, annual, shrub-like herb, 3 - 10 feet tall.
    - Stem - Stout, thick, reddish, green, or purple.
    - Leaves - Alternate, simple, large, palmately veined and lobed, peltate, 4 - 32 inches in diameter. Petiole is stout.
    - Flowers - Imperfect, unisexual, in clusters, no petals; calyx is 3 - 5 parted; no corolla, stamens are numerous and ovary is 3 celled.
    - Fruit - Capsule - 3 seeded, spiny. Seeds - 1 cm long, smooth and glossy, black or mottled with grey or brown.

Habitats

- Native to tropics (Africa), now commercially grown in the USA in Illinois, Missouri, Kansas, Oklahoma, Oregon and California.
- Naturalized in the south, i.e., Texas, where winters are mild. Occurs in disturbed areas, roadsides, dumping grounds, barnyards of warmer areas of USA but confined to planted sites in cooler areas.
- Used as ornamental outside in summer in midwest, etc., and less often as a houseplant.
- Toxicosis not only associated with plant, but most often with seed and seed products.

Toxic Principle

- Ricin is the principal toxin, and is a phytotoxin (a lectin, also termed a toxalbumin). Toxalbumins are very toxic proteinaceous compounds of plant origin.
- Ricin is 100 times less toxic orally than parenterally; the difference is apparently not a result of the effects of trypsin or pepsin.
- Orally, ricin is readily absorbed from the stomach and intestine.
- Ricin is water soluble and not present in castor oil.
- Being a protein, and a fairly large molecule, ricin is heat labile. In castor bean cake, meal, etc. the ricin is generally inactivated by heating. Aging also reduces toxicity.
- Ricin may comprise up to 3% of the seed weight.
- Another phytotoxin in castor bean, ricinine, is reportedly goitrogenic. The importance of this compound is not clearly established.

Toxicity

- LD_{50} in the rabbit is 40 μ g/kg, which indicates that ricin is one of the most toxic compounds of plant origin.
- Cattle: 14 ounces of beans may be lethal, beans at 0.2% of BW may cause toxicosis.
- Horses: Even more susceptible than cattle, beans at 0.01% of BW may cause toxicosis.
    - **Note - The susceptibility of sheep and hogs approximates that of cattle. Also, small animals are quite susceptible.**
- Humans: One to 3 beans may be lethal.
- Ducks: The LD_{50} in ducks approximates 3 - 4 beans.
- Hens: Are fairly resistant to ricin.
- Poultry general: Beans at 1.4% of BW may cause toxicosis.
- All parts of the plants are toxic, but especially the seeds.
- Acts as an antigen and protective antibodies may be elicited. Primarily of research rather than practical importance.

- Seeds, presscake or meal (if inadequately processed) and foliage are poisonous.
- Castor oil is not poisonous.
- "Presscakes" from castor beans alone or mixed with linseed cakes have caused the most problems in cattle. Ricin is also excreted in the milk, which can cause it to have purgative properties.
- It has been suggested that anaphylactic reactions may occur in all species.

Mechanism of Action

- Binds to galacto-lipid and galacto-protein components of plasma membranes which leads to toxin internalization and cell death.
- In some cell types, at least in rodents, a second mechanism of toxin internalization relies on binding of mannose components in the ricin molecule (mannose receptor on the cell membrane).
- Protein synthesis inhibition by the A-subunit of ricin. Reported mechanisms of ricin are enzymatic de-adenylation of ribosomal RNA, and thus inactivation of 60S ribosomes.
- Recent studies suggest that the primary action of ricin is to act via a ribonuclease activity.

Signs

- Signs appear after a characteristic lag period of a few hours to days, usually onset is between 12 hours and 48 hours.
- Nausea, gastrointestinal irritation, abdominal pain, diarrhea which is often bloody, tenesmus, dehydration and at postmortem severe inflammation of the stomach and intestine.
- Anorexia, cessation of rumination.
- Excessive thirst.
- Weakness, muscle twitching.
- Dullness of vision, convulsions, dyspnea, opisthotonus, coma and death.
- Sometimes clonic convulsions and decreased tendon reflexes are described.
- After convulsions, death may result from paralysis of the respiratory center - artificial respiration may not preserve life for long because of rapid onset of concurrent vasomotor paralysis.
- Clotting time may be prolonged, possible hypoprothrombinemia.
- Cyanosis.
- In ducks, there is an ascending paralysis which may be confused with botulism.
    - Sometimes thousands of ducks are poisoned. Also geese.
- Horses:
    - Trembling, sweating, dyspnea, incoordination.
    - Vigorous heart contractions.
    - Shivering, cold extremities.
    - Depression, increased body temperature.
    - Weak pulse.
    - Constipation or diarrhea, convulsions.
- Cattle:
    - Diarrhea stained with blood.
- Pigs:
    - Frequent vomiting.
- Poultry:
    - Depression.
    - Roughened feathers, droopy wings.
    - Greyish wattles and combs.
    - Egg production ceases.
    - Moulting may begin.
    - Emaciation.
    - Death.
- Humans:
    - Chewing may cause burning sensation in mouth and pharynx.
    - Vomiting and severe abdominal pain.
    - Diarrhea, thirst, and blurred vision.
    - Perspiration, trembling, weakness.
    - Convulsions and death.

Clinical Pathology and Lesions

- There may be leukopenia and a left shift at about 16 hours postdosing.
- Phytotoxins may cause hemagglutination but this has not been demonstrated to be a reliable finding in the field.
- Hypoglycemia possible.
- Catarrhal to hemorrhagic gastroenteritis.
- There may be petechial serosal hemorrhages on the viscera in body cavities and in the subepicardium.
- Lesions in the liver and kidney generally include swelling and in birds, yellow discoloration (fatty liver) and hemorrhage.
- Mesenteric lymph nodes are usually edematous.
- Pulmonary edema sometimes occurs.

Diagnosis

Identification of *Ricinus* or products thereof, evidence of consumption and appropriate signs and lesions.

Treatment

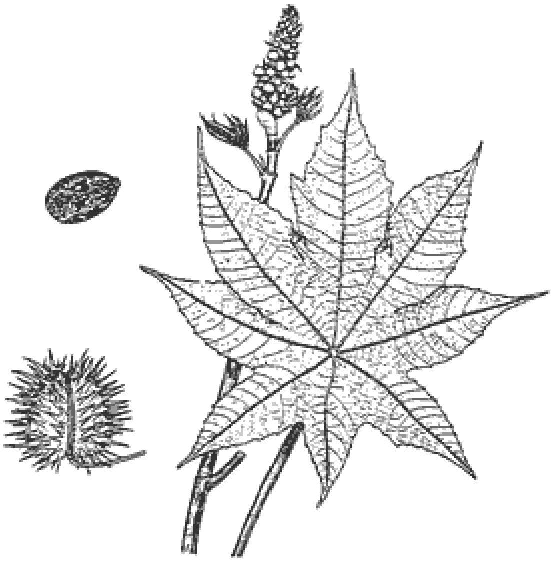
- Early - Use an emetic in appropriate species followed by activated charcoal and a saline cathartic unless contraindicated; e.g., due to marked diarrhea.
- A gastrointestinal tract protectant such as kaolin-pectin and fluid therapy are used as indicated. Appropriate fluid and electrolyte therapy can greatly increase chances of survival.
- Ricin is not dialyzable.
- Judicious use of anticonvulsants if indicated.
- Monitor renal and hepatic function and electrolyte - Fluid balance.
- Maintain (or establish) respiration, fluid, and electrolyte balance.
- Oral antacids to alleviate local irritation. Ascorbic acid increases survival rates.
- Forced alkaline diuresis has been suggested to prevent nephrosis.

Prevention

- Do not plant castor bean plants where animals (or children) may have any access whatsoever.
- Clip heads before they mature when used as an ornamental.
- Moist heat destroys ricin, but does not prevent allergic reactions to castor oil.
- Allow castor-oil-cake to stand or heat treat before feeding.

Comments

- True immunity may be produced through increasing doses of the poisonous principle.
- Passive immunity may be conferred by the injection of antisera.
- Castor bean poisoning in USA is infrequent.
- Wild and cultivated castor beans are of the same species and both are toxic.



Castorbean - Note the large digitately lobed leaves, the clusters of male flowers (above) and female flowers (below) on the seed stalk, and the spiny seed pod and mottled seed (enlarged, lower right).

Robinia

Robinia pseudoacacia - Black or yellow locust, false acacia
R. viscosa - Clammy locust

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Horses, cattle	Hours	Days, potentially lethal	

Familly - Leguminosae (pulse or bean family)

Description

- Plant - A small tree but sometimes up to 75 feet tall, deciduous.
- Stem - Trunk straight, long, slender, coarse, brown bark, spines are scattered on young branches and are unbranched resembling large rose thorns.
- Leaves - Alternate, pinnately compound, spikes short 1/4 - 1/2 inch long, unbranched; leaflets are entire, elliptical, opposite and in 3 - 10 pairs, 1 - 2 inches long.
- Flowers - Leguminous, white, showy, racemous, drooping 4 - 8 inches long, with 5 petals, irregular and white. Five sepals and 10 stamens.
- Fruit - Pods, thin, brown, 2 - 4 inches long, straight, flat and many seeded.

Habitat

- Eastern and central USA, southern Canada.
- Native to the central-eastern states.
- Dry woods, thickets, roadsides, sometimes forms dense stands in clearings and old pastures.
- Occasionally placed as an ornamental.

Toxic Principle

- The heat labile, phytotoxin, robin.
- Also the phytotoxins robitin and phasin.
- Glycosides are also present such as robitin as is the alkaloid, robinine, however generally the phytotoxin (toxalbumin) robin is regarded as the primary compound involved.

Mechanism of Action

Protein synthesis inhibition by the toxalbumins.

Toxicity

- Black locust is not necessarily always toxic; fatal cases are rare but recovery requires several days or weeks. The flowers are not toxic, but the bark, sprouts, pods and foliage are all toxic. Livestock are most often poisoned because of stripping off of bark (especially when they are tied to the tree), or from grazing on sprouts or from eating small branches from recently felled trees.
- Horses:
  - 0.1% of body weight (BW) of aqueous bark extract is toxic; also 0.04% of BW of powdered bark is toxic.
- Cattle:
  - Cattle are about 1/10 as sensitive as horses.
- Poultry:
  - Have been poisoned by eating leaves.
- Children:
  - Have been poisoned by sucking young twigs.
- Sheep:
  - Are also sometimes poisoned.

Signs

- Delay of 1 - 1.5 hours before onset of clinical effects.
- Anorexia, lassitude, stupor and depression, or hyperexcitability.
- Weakness (posterior paralysis in horses and cattle).
- Laminitis in horses.
- Nausea and vomiting.
- Coldness of extremities.
- Pupillary dilation.
- Dyspnea, tachycardia, weak and irregular pulse.
- Diarrhea which may be bloody, or constipation.
- Fatalities are rare but may occur within 2 - 3 days.

Lesions

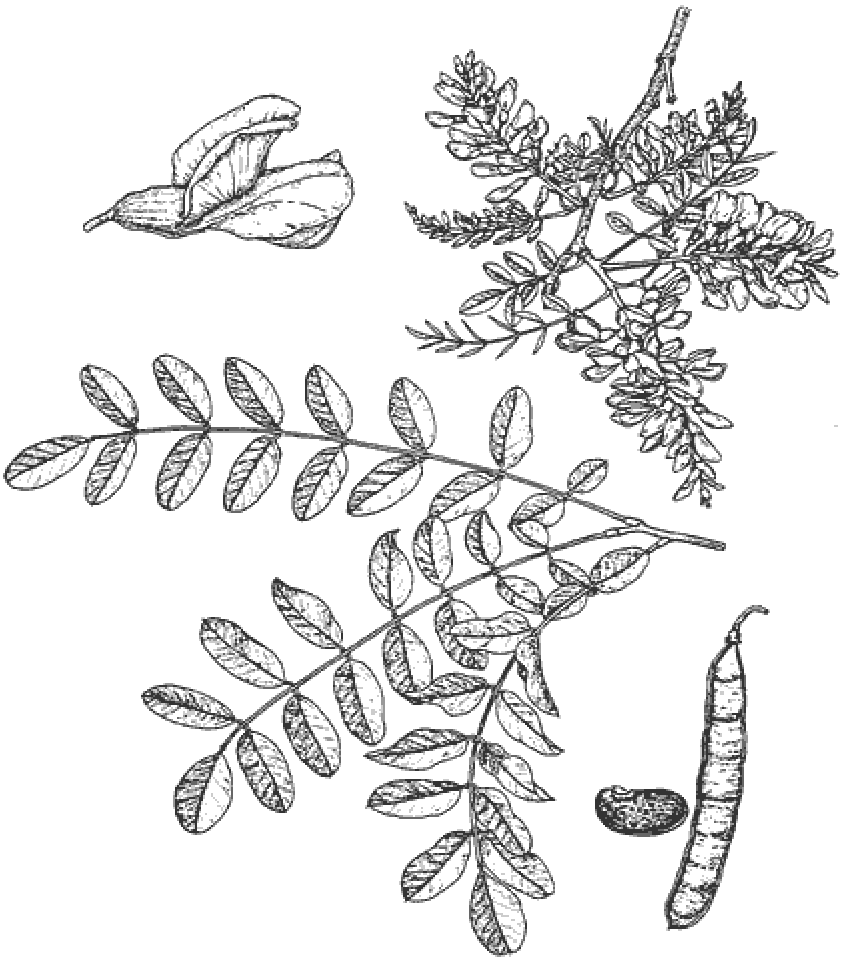
- Inflammation and edema of the mucosae of the digestive tract.
- Poultry exhibit degenerative changes in the liver and kidney.

Diagnosis and Treatment

See *Abrus precatorius*.

Comments

Of 32 boys who ate inner bark of black locust fence posts in 1887, 2 were severely poisoned and became stuporous; however all eventually recovered.



Black Locust Note the pendulous flower clusters and flower (enlarged, upper left), the pinnately divided leaves, and the flattened pod and enlarged seed (lower right) of this popular ornamental tree.

Phoradendron spp. and *Viscum* - Mistletoe

P. serotinum - The American mistletoe used most for Christmas mistletoe, also called false mistletoe

P. rubrum

P. tomentosum

P. macrophyllum

Viscum album - European mistletoe or mistletoe

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Small animals	Hours	Days, potentially lethal	

Description

A semiparasitic evergreen shrub with greenish branches which form a dense bushy growth 1 - 4 feet in diameter. Leaves are opposite and simple, oblong to ovate and 0.5 - 1.5 inches long. Fruit is a small white or whitish-pink berry which covers a short spike at the base of the leaf.

Habitat

- Commonly parasitize oak, walnut, or other deciduous trees, southeast New Jersey to Florida west to Illinois and Texas, also in the far western USA.
- *P. serotinum* - Brought inside for Christmas season. Some have plastic berries in place of natural ones.

- *P. rubrum* - Southernmost Florida, Caribbean islands.
- *P. tomentosum* - Kansas to Louisiana, west to Texas and into Mexico.
- *Viscum album* - Sonoma County, California (originally imported from Europe: apparently not imported for Christmas; the primary mistletoe in Europe).

Toxic Principle

- *Phoradendron* spp. contain:
    - Phoratoxin, a toxic lectin (toxalbumin). Inhibits protein synthesis at the ribosomal level.
    - Amines of beta-phenylethylamine, choline, and tyramine (probably of less importance than the toxalbumin. Three or more berries are possibly lethal for a child.

Viscum album:

- May decrease blood pressure due to a cholinomimetic effect.
- Viscumin - Toxic lectin (toxalbumin).
 - agglutinates RBCs *in vitro*.
- Viscotoxin - Peptide with properties similar to viscumin but may also stimulate skeletal muscle and smooth muscle possibly by a direct effect. Some effects of viscotoxin are reversible *in vitro* by addition of calcium (apparently not tested *in vivo* at this time).
- Polysaccharides - Potential anticancer drugs.
- Commercial products (drugs) from *Viscum* spp.
    - Iscador ® - An "immunomodulatory" agent.
    - Helixador ® and Plenosol ® - Agents used most to alleviate human hypertension.

Toxicity

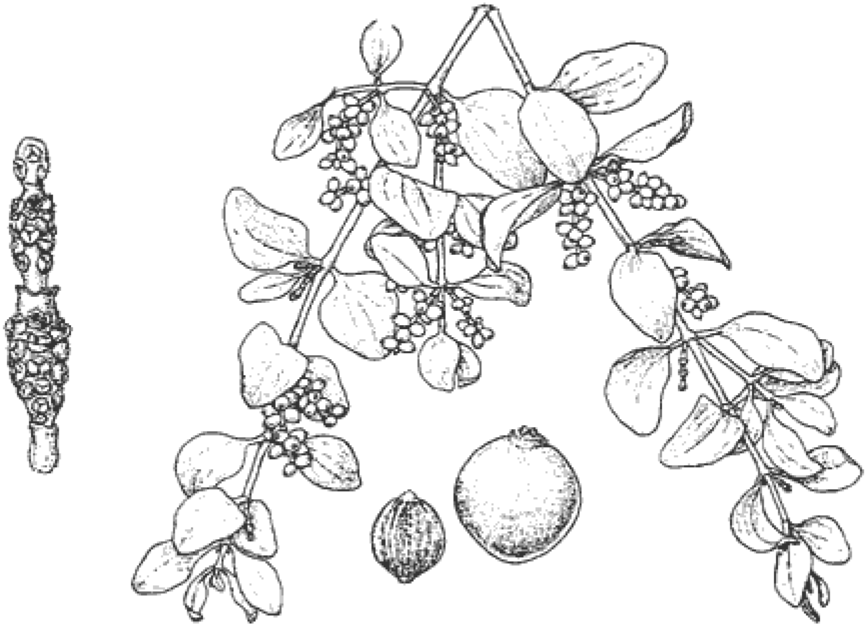
Potential cause of sudden death in browsing animals.

Signs

- Acute gastrointestinal upset, vomiting, nausea, diarrhea. The acute gastroenteritis may occur after a delay of several hours.
- Hypothermia.
- Polyuria.
- Mydriasis.
- Lay persons have used mistletoe as an abortifacient in humans which has led to poisonings and several fatalities. Does increase tonus of uterine muscle.
- Delirium, ataxia, coma or hyperesthesia, seizures, and opisthotonus may occur.
- Dyspnea.
- Bradycardia (may have adrenergic override with resultant tachycardia).
- Cardiovascular collapse with asystole (sometimes described as "digitalis-like") may occur with mistletoe toxicosis. Decreased blood pressure associated with *Phoradendron* in humans. It is unclear whether the cardiovascular collapse may be due solely to fluid and electrolyte losses related to digestive tract upset.
- Hemolysis sometimes in humans with *Viscum* poisoning.
- If death occurs, it usually takes place at approximately 10 - 16 hours after ingestion.

Treatment

- Removal of mistletoe from GI tract: emetic, lavage, enterogastric lavage (as conditions permit).
- Activated charcoal, saline cathartic.
- Atropine.
- If cardiac effects predominate treat symptomatically and supportively and **only if signs fit** should the veterinarian treat as for digitalis overdose and then with careful monitoring.
- Support: measures to correct fluid/electrolyte imbalances.



Oak Mistletoe (*phorodendron coryae*) - The paired oval leaves, the flowers embedded in the flower stalk (upper right), and the white sticky berries and grooved seeds (enlarged, lower center) are characteristic of this parasitic plant.

Irritant Oils

Ranunculus spp. - Buttercups

R. sceleratus - Cursed crowfoot
R. abortivus - Small flowered buttercup
R. bulbosus - Bulbous buttercup
R. repens - Creeping buttercup
R. acris - Tall field buttercup

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Herbivores	Hours	Days; infrequently lethal, poisoning is rare	

Familly - Ranunculaceae (crowfoot family)

Description

- *R. abortivus*
    - Buttercups (also called Crowfoot plants) are erect, except for one creeping species.
    - Six inches to 2 feet tall with hollow stems.
    - Perennial or annual herbs with 2 kinds of leaves: petioled basal leaves, palmately arranged, roundish, with scalloped edges; and alternately placed stem leaves that are stalkless, deeply divided and made up of 5 narrow lobes, often 3 pointed.
    - Solitary flowers are yellow, 1/4 inch or less in diameter, and have 5 petals and 5 sepals. After the flowers wither, numerous seeds form uniovular heads at the top of the flower stalks.
    - Other common species are similar, except that the ditch buttercup (also called cursed crowfoot) has divided basal leaves. Other species have larger flowers and 3 lobed leaves.

Habitat

- Throughout the world and United States, but most problems occur in the northern USA and Canada.
    - *R. sceleratus* - Northern USA and Canada, low wet places and marshes.

    - *R. abortivus* - Eastern USA, pastures and open woodlands: The most common species in Illinois.
    - *R. bulbosus* - Northeastern USA, meadows and pastures.
    - *R. repens* - Northern USA and Canada, Pacific coast, infrequent or locally common in low wet pastures and meadows.
    - *R. acris* - Eastern USA and from western British Columbia southward to Oregon, pastures and meadows.

Toxic Principle

*Ranunculus*spp. contain the glycoside, ranunculin from which the poisonous principle, protoanemonin is released when the plant is crushed by virtue of enzymatic action which is activated by crushing. Protoanemonin is a volatile, yellow oil with a lactone moiety which is extremely prone to undergo spontaneous polymerization to yield the innocuous anemonin. Protoanemonin is a bitter tasting oil.

Susceptible Species

Cattle are more susceptible but horses, goats, and swine also may be poisoned.

Toxicity

- Plants contain 0.3% - 2.5% protoanemonin on a dry weight basis.
- The highest concentration of protoanemonin is present at the beginning of flowering.
- Protoanemonin is volatile, so it does not present a problem in hay.
- Most poisoning occurs in spring and early summer.
- The poisonous principle produces blisters if in contact with the skin.
- Relatively large amounts of the plant must be consumed before livestock develop toxicosis.

Signs

- General:
    - Salivation, reddened oral mucous membranes (may be severe).
    - Severe gastric irritation, colic, abdominal pain, anorexia.
    - Diarrhea or black fetid feces.
    - Depression or excitement, muscle trembling, twitching of the ear and head muscles, which may proceed into general excitement and convulsions or "paralysis".
    - Bradycardia.
    - With exposure to *R. acris* blisters and inflammation around the mouth and gastric pain as well as vomiting may occur. Diarrhea may follow and muscle spasms may occur. Temporary blindness and convulsions may also occur.
    - Swine:
        - May become prostrate and remain down for 2 - 3 days before death.
    - Sheep:
        - Acute death.
    - Cattle:
        - Bitter milk or reddish discoloration of milk from exposed cows. Blood stained urine and blindness have occasionally been reported.

Lesions

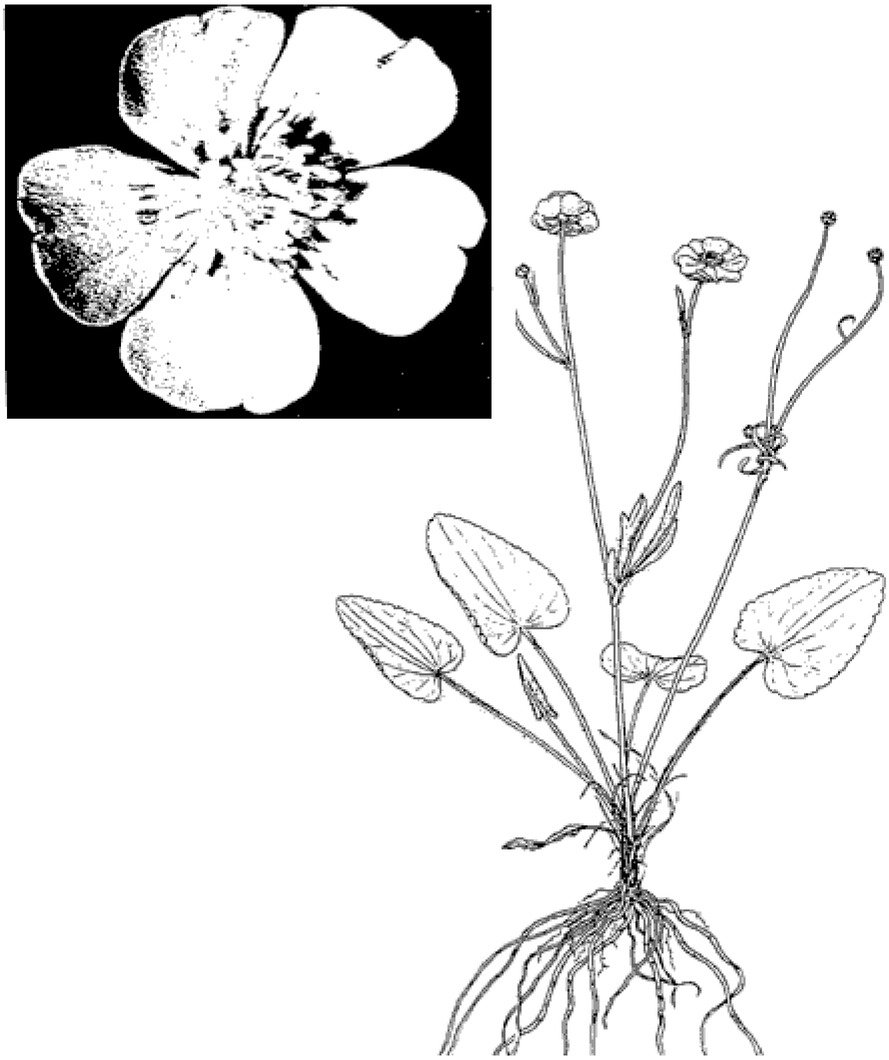
- Oral tissues may be fiery red.
- Severe inflammation of the stomach and intestinal tract.
- Hemorrhage into the lumen of the digestive tract.
- Pulmonary congestion and ecchymoses.

Diagnosis

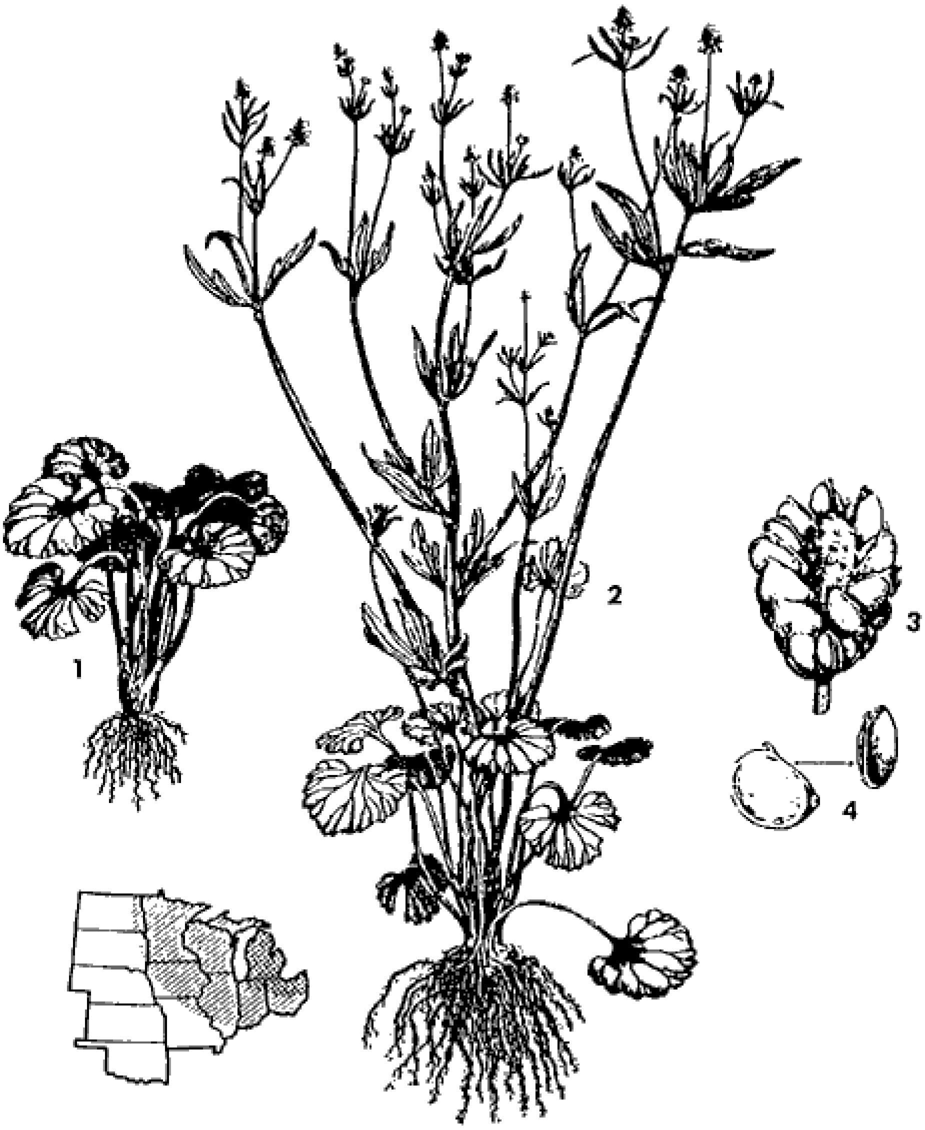
Identification of *Ranunculus*, evidence of consumption and appropriate clinical signs and lesions.

Treatment

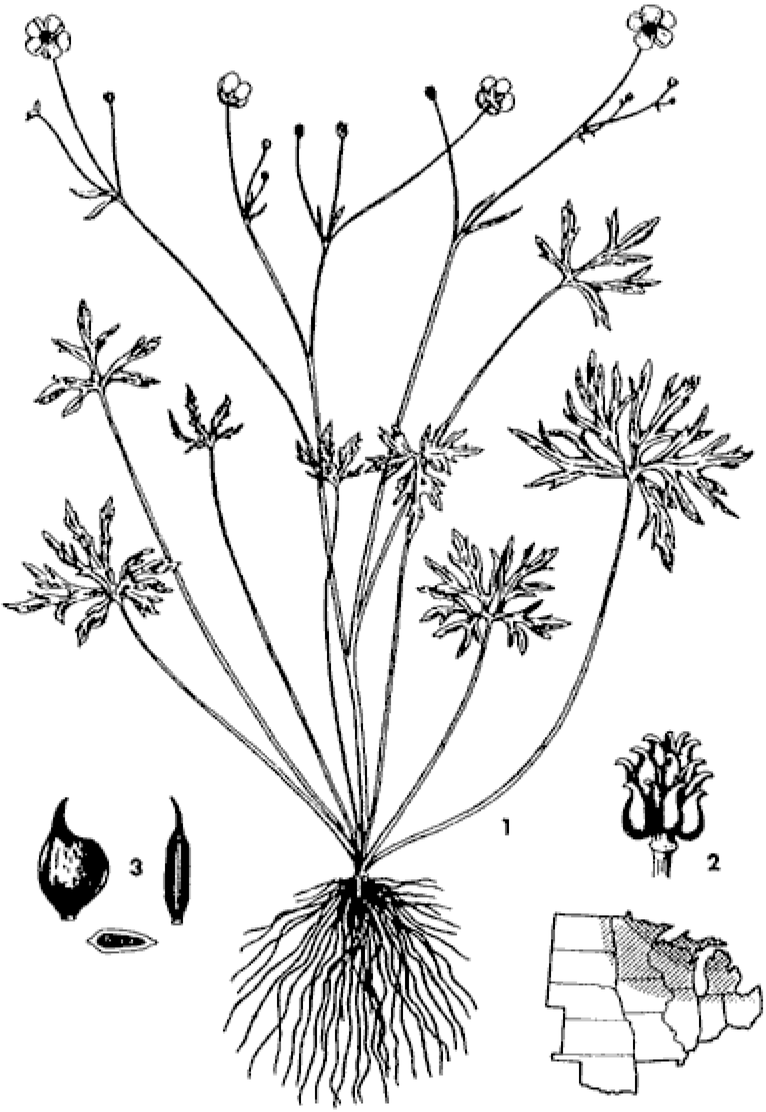
- Dilution with milk and egg white are recommended and if burns are not severe it may be appropriate to use an emetic or lavage depending on species and the absence of clinical signs. Activated charcoal with a saline cathartic should be given. Appropriate supportive care to control dehydration, electrolyte imbalance, etc. may be indicated.
- **Note** -
  - American Indians considered the seeds harmless and used them for food.
  - Due to the almost immediate onset of the irritant action, animals tend to avoid the plant; however some animals seem to develop a liking for buttercup.



Buttercup - Colorful, usually yellow, flowers and large basal leaves are characteristic of this herb.



Smallflower Buttercup, *Ranunculus abortivus* L. - **1**, young plant; **2**, plant in bloom; **3**, mature receptacle bearing seeds; **4**, seeds. **Annual** or **biennial**, reproducing by seeds. **Stems** slightly hairy, slender, branched from base, 6 to 20 inches (15 to 50 cm) tall. **Lower leaves** round, bright green with round-toothed margins, borne on long petioles coming from base of plant. Upper leaves on shorter petioles, divided into 3 to 5 leaflets with somewhat toothed margins. **Flowers** small, yellow, with small oblong petals. **Seeds** produced in round heads, numerous, flattened with very small curved beak, dull, wrinkled, yellowish-brown. **Found** in lowland meadows, pastures, and fields. The plant has no forage value and may poison livestock.



Tall Buttercup, *Ranunculus acris* L. - **1**, plant in bloom; **2**, seed head; **3**, seeds. **Perennial**, reproducing by seeds. **Stems** erect, branched above, hairy, 1 to 3 1/2 feet (30 to 106 cm) tall. **Leaves** alternate, hairy, palmately divided into narrow segments. **Flowers** usually bright yellow but sometimes cream-colored, with 5 to 7 petals. **Seeds** numerous, dark brown, about 1/8 inch (3 mm) long, minutely pitted, flattened, with hooked beak; formed in a rounded head. **Found** in pastures; does not persist in cultivated crops. This plant contains an acrid juice which is somewhat poisonous if eaten by livestock, often blistering the mouth and intestinal tract.

Caltha - Marsh Marigold

Caltha palustris - Marsh marigold, cowslip
C. natans

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Herbivores	Hours	Days; infrequently lethal, poisoning is rare	

Familly - Ranunculacea (Crowfoot family)

Habitat

Worldwide distribution in the northern hemisphere; native in the northeastern USA, Canada to Alaska and south to Virginia, westward to Iowa. Swamps and wet meadows.

Toxic Principle

Very acrid plant, contains protoanemonin (see Ranunculus handout for signs, lesions, treatment). May also contain an alkaloid and a glycoside.

Toxicity

- Fresh tops are poisonous, also stems.
- Dried or thoroughly cooked plant is reportedly not toxic.
- All parts may be toxic.
- Apparently distasteful to livestock.
- Dermatitis may result from prolonged contact.

Note - Most marigolds are not regarded as toxic, thus marsh marigold is an exception.

Saponin - Contaning Plants

Phytolacca - Pokeweed

Phytolacca americana - Pokeweed, scoke, garget, pigeonberry
(P. decandra)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Herbivores	Hours to days	Days, potentially lethal	

Familly - - Phytolaccaceae (pokeweed family)

Description

- *P. americana*
    - Plant - Tall, distinctive, perennial herb, 9 feet tall, strong smelling.
    - Stem - Stout, glabrous, purple or green, very branched, smooth, succulent, 3 - 10 feet tall.
    - Leaves - Alternate, petiolate, entire, ovate, simple, regular, base and tips are acute, no stipules, 5 inches long, red veined.
    - Flowers - Inflorescence racemose, terminal, drooping; flowers numerous, small, white, or greenish; no petals, 4 - 5 sepals, white or greenish, 10 stamens, separate, ovary superior.
    - Fruit - Ten seeded, inky crimson juice, shiny, purple berry, in grape like clusters but with more rigid stalks and more space between the berries, large, lenticular, glossy, black with endosperm.
    - Rootstalk - Large, fleshy, thick, taproot.

Habitat

Maine and Ontario to Florida, Texas and Arizona. Common in recent clearings and open places in woods, along borders of woods, barnyards, lowlands, roadsides and especially rich moist soils.

Toxic Principle

- Saponins, believed to be the primary toxic constituents, are present in the berry juice and other parts.
- Other toxic constituents have also been identified including the alkaloid phytolaccine (in small amounts) and the alkaloid phytolaccotoxin, as well as a glycoprotein.

Mechanism of Action

- Saponins presumably dissolve cell membranes. *In vitro* they are used as hemolysins.
- Saponins are bitter tasting and have tendency to cause (honeycomb) foaming in water.

- Saponins are glycosides. Because the aglycone moiety is nonpolar, while the carbohydrate moiety is water soluble, they have strong detergent properties.

Susceptible Species

Cattle and sheep, but occasionally poisoning occurs in horses, goats and swine.

Toxicity

- All parts of the plant are toxic, especially the roots, shoots and unripe berries.
- The toxicity of the berries decreases as they mature.
- In some species, the emetic dose of powdered root is about 1 gm.
- Fatality has resulted from consumption of the root.
- In man, 10 raw berries may cause serious toxicosis.
- Two or 3 uncooked berries may be fatal to a child.
- The seeds are almost as poisonous as the roots.
- Dilution and possibly degradation in the rumen may explain the absence of some of the toxic effects seen in ruminants.
- The consumption of young shoots is widely regarded as safe provided that they are boiled, with 2 changes of the water.
- The plant is regarded as bitter and therefore unpalatable to animals.
- Poisoning is rare, but occurs in the spring when roots may be pulled and when forage is scarce.

Signs

- Burning sensation in the mouth immediately after consumption.
- Other signs usually commence about 2 hours after consumption.
- Nausea, vomiting, severe cramps, watery diarrhea (often bloody).
- Weakness.
- Blurred vision (humans).
- Dyspnea, perspiration.
- Spasms, prostration, tremors.
- Terminal convulsions, may be present and death reportedly due to respiratory paralysis may occur in about 6 hours.
- Swine:
  - Unsteadiness, inability to rise, wretching.
  - Jerking movements of the legs.
  - Subnormal temperature.
- Cattle:
  - Same general signs plus a decrease in milk production.

Lesions

- Mild to severe gastroenteritis, local hemorrhagic, sometimes ulcerative gastritis is worst lesion. Congestion of the liver, dark discoloration and swelling.
- Peripheral blood plasmacytosis has been reported.

Diagnosis

Identification of *Phytolacca*, evidence of consumption and appropriate clinical signs and lesions.

Treatments

- Evacuation of the gastrointestinal tract, activated charcoal and a saline cathartic.
- Control dehydration, seizures, and if necessary institute artificial respiration.

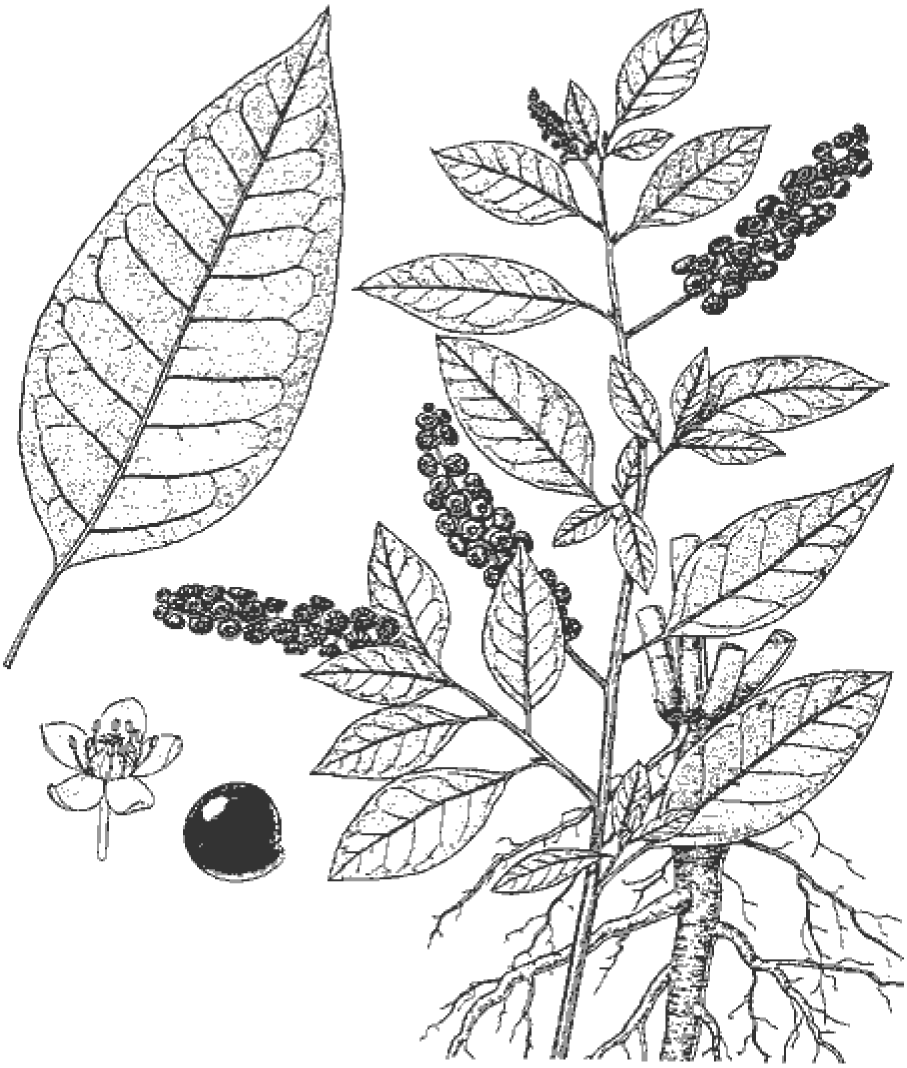
Prevention

- Eradicate the plant; burning, pulling.

- Plant corn or soybeans on the area for at least 2 years.
- 2,4-D when plants are young.

Comments

- Young shoots may resemble and taste like asparagus.
- In 1965, it was considered by some to be the most common plant poison in children.
- The juice of the berries has been used as a magenta dye, hence the name ink berry.
- The berries, when ripe, have been used by some persons in the making of pies.
- Severe incidents of poisoning in swine have been reported in Indiana and Alabama.



Pokeweed - The large, oval, pointed leaves; clusters of flowers (single flower, enlarged, lower left); purplish fruits; and shiny black seed (enlarged, lower left) are characteristic of this attractive, but poisonous, plant.

Saponaria spp.

Saponaria officinalis - Bouncing bet, soapwort
Saponaria vaccaria - Cow cockle

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Herbivores	Hours to days	Days, potentially lethal	

Familly - Caryophyllaceae (pink family)

Description

- *S. vaccaria*
  - Plant - Glabrous, erect, annual herb.
  - Stem - Jointed, opposite, branched.
  - Leaves - Entire, glaucous, palmately veined, ovate to lanceolate, no petioles.
  - Flowers - Conspicuous in terminal cymose clusters; petals pale red; calyx of 5 sepals, green, tubular, 5-toothed, 5 angled; corolla has 5 petals, white, pink or faint red; 10 stamens, 2 styles.

Habitat

- Introduced from Europe and is present throughout the northern USA as a weed, especially in northwestern USA and western Canada. Found in spring wheat and flour containing screenings.
- Bouncing bet is a perennial weed found in roadsides and waste places.
- Cow cockle is an annual, which is troublesome in grain crops of NW USA.

Toxic Principle

- Both plants contain large amounts of saponins, which froth when extracted with water. The saponins are soluble in water and alcohol.
- The sapotoxins of these saponins are similar or identical to those of corn cockle (*Agrostemma githago*).
- Hydrolysis of the saponins yields sugars and sapogonins, a group of physiologically active substances.

Toxicity

- The toxic material is contained in highest concentration in the seeds. Most animals refuse to eat the seeds and avoid grains or screenings containing them.
- Feeding of the plant itself to sheep in an amount of 3% of the BW caused death within 4 hours; the plant weight being expressed on a dry-weight basis.

Signs

- Irritation of the digestive tract, vomiting, nausea, diarrhea.
- Slowed or rapid breathing.
- Unsteadiness, ataxia, coma.

Diagnosis

Identification of *Saponaria*, evidence of consumption, especially of seeds (microscopy of feed and/or stomach contents), appropriate clinical signs and lesions.

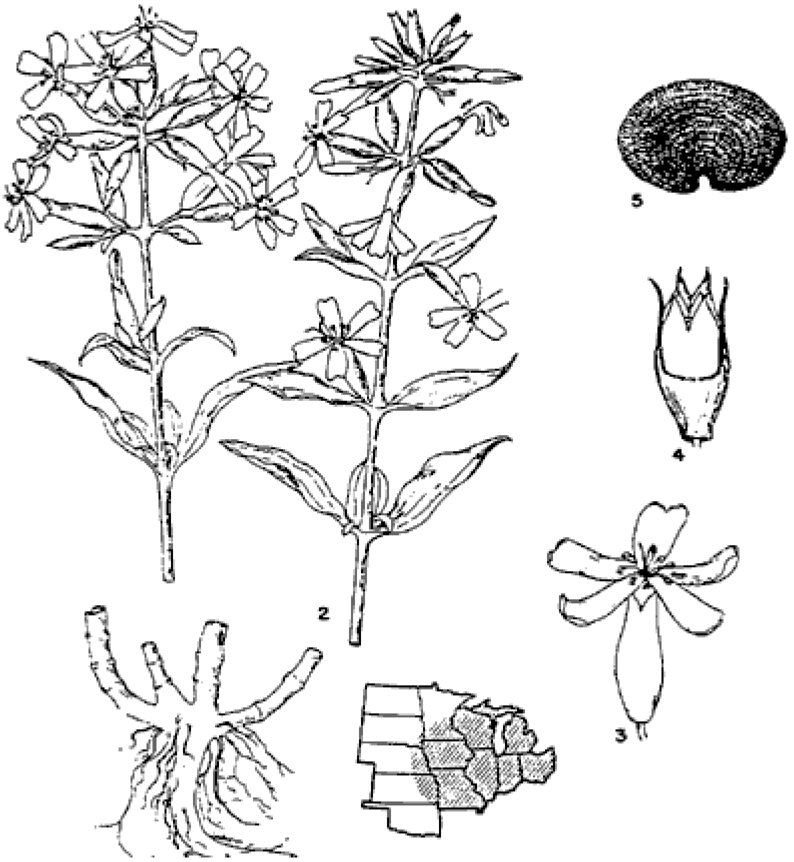
Treatment

Evacuate gastrointestinal tract, activated charcoal and a saline cathartic, demulcents, supportive therapy.

Comment

Poisoning is very rare.

Pink Family, *Caryophyllaceae*



Bouncingbet, *Saponaria officinalis* L. - **1**, lower part of plant; **2**, flowering stems; **3**, flower; **4**, mature seed pod with part of calyx removed; **5**, seed. **Perennial**, reproducing by seeds and short rhizomes. **Stems** stout, jointed, erect, 12 to 24 inches (30 to 60 cm) tall, clustered, smooth, and usually unbranched. **Leaves** opposite, smooth, entire, 2 to 3 inches (5 to 7.5 cm) long, about 1 inch (2.5 cm) wide, without petioles. **Flowers** in conspicuous clusters at the tops of the stems; about 1 inch (2.5 cm) across with 5 pink or white petals, and with base enclosed in a tubular calyx about 3/4 inch (1.9 cm) long. **Seed pod** narrowly egg-shaped, pointed, containing numerous seeds, enclosed by calyx. **Seeds** flattened, dull black, kidney-shaped, about 1/16 inch (1.5 mm) long, surface covered by curved rows of minute knobs. **Found** along roadsides, in waste places, and on ditch banks. Originally grown in gardens as an ornamental, from which it has spread. In pioneer days, used as a soap substitute, the stems and rhizomes making a foamy solution when bruised in water.

Agrostemma Githago - Corn Cockle

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Herbivores	Hours to days	Days, potentially lethal	

Description

- A conspicuous tall, silky, grayish winter annual (starting growth from seed in the fall, maturing and forming seed and dying the next summer), to 3 feet tall.
- Leaves opposite, 2 - 4 inches long, without petiole or stipules, linear to lanceolate; stems and leaves bearing a conspicuous covering of white hairs.
- Flowers showy, solitary, about 1 in. across, terminating long slender pedicels; calyx 5-parted, conspicuous; corolla of 5 pink to purple petals.
- Fruit a capsule, bearing numerous black seeds each about the weight of a wheat grain.
- Seeds covered with rows of small warts.

Habitat

- Introduced from Europe and found throughout the United States as a serious weed of cultivation wherever winter wheat is grown.
- Occasionally found in winter rye and other crops and on roadsides.
- Selected strains are cultivated in flower gardens.

Toxic Principle

The sapogenin githagenin is contained in the seeds and amounts to 5 - 7% of their weight.

Toxicity

- A lethal dose in cattle and hogs was about 0.1 - 0.25% of the animal's weight of ground seed and about twice that of whole seed indicating that the seed coat may have reduced the rate or extent of absorption.
- The incidence of poisoning has been almost eliminated by modern harvesting machinery that removes the seeds.
- The primary hazard lies in the feeding of wheat screenings.

Signs

- Gastrointestinal upset, severe gastroenteritis.
- Poultry usually avoid but 0.2 - 0.5% of BW of seed is lethal to young birds.
- Older birds are somewhat more tolerant.
- Poisoned birds develop a "cheesy" exudate in the mouth and diarrhea.
- Horses and cows have been lethally poisoned.

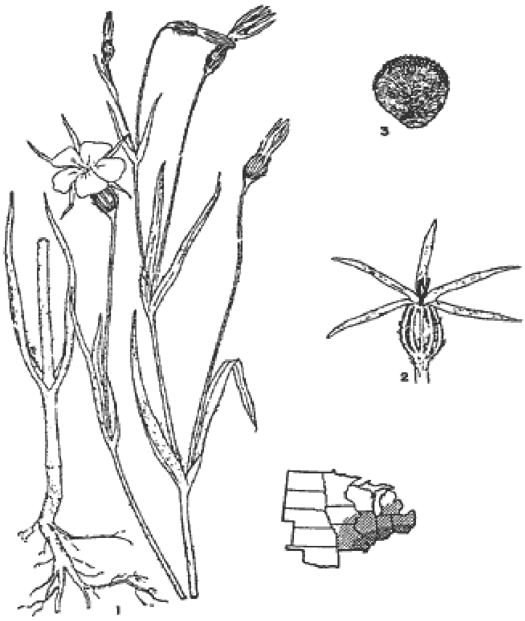
Diagnosis

Feed microscopy (I.D. seed) plus appropriate signs and lesions.

Treatment

See Saponaria handout.

Pink Family, *Caryophyllaceae*



Corn Cockle, *Agrostemma githago* L. - **1**, plant in flower; **2**, seed pod enclosed by the ribbed calyx; **3**, seed. **Winter annual**, reproducing by seed. **Taprooted**, shallow. **Stems** rough, hairy, erect, 2 to 3 feet (60 to 90 cm) tall, swollen at joints, branching slightly. **Leaves** opposite and jointed at base, slender, hairy. **Flowers** large, purple, with narrow, green sepals longer than colored petals. **Seed pod** holding several seeds, enclosed in a 10-ribbed urn-like calyx. **Seeds** black, about 1/8 inch (3 mm) in diameter, triangular, covered with rows of sharp tubercles. Seed poisonous and therefore highly objectionable in grain used for milling or feed. **Found** especially on cultivated land and in association with fall-sown grain crops.

Hedera Helix - English Ivy

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Most species	Hours to days	Days, potentially lethal	

Description

- Common cultivated vine used as ground cover, on sides of buildings as house plant or standing erect as a shrub.
- Leaves - Typical plants have dark green, leathery, 3 - 5 lobed, maple-like leaves. Horticultural forms may possess round or sometimes long lobed leaves often with white streaks or predominantly white coloration with green streaks.
- Flowers - Inconspicuous whitish to greenish flowers in small round clusters appearing late in the growing season.
- Roots - Anchoring aerial roots may be noted in plants that grow up the sides of buildings.
- Fruit - Persistent, pea-size, black, bitter-tasting berry with 3 - 5 seeds.

Habitat

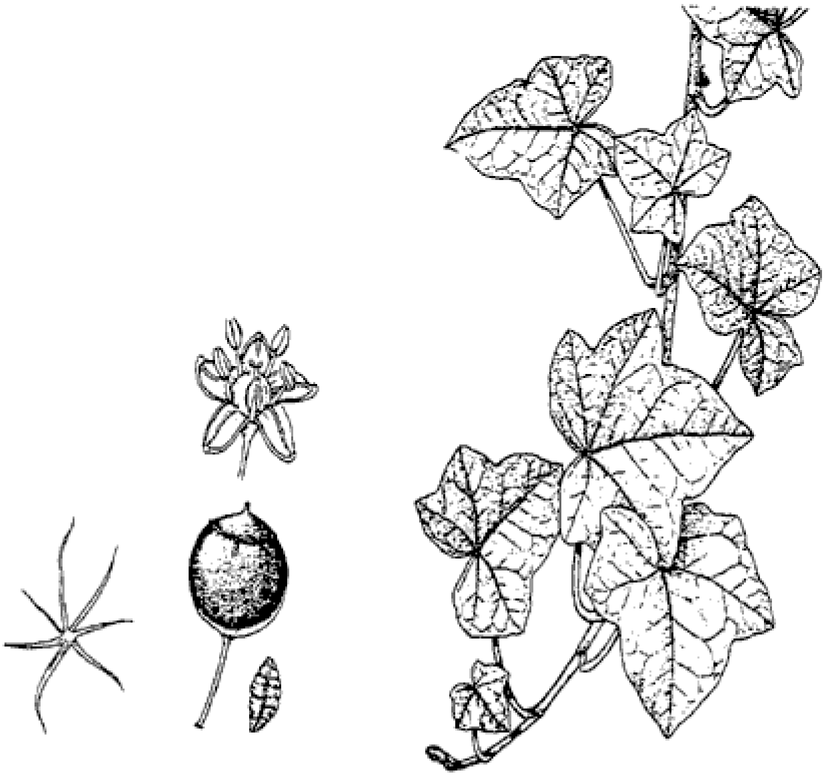
- Grows hardily throughout most of the USA.
- Potted varieties are common indoors.

Toxic Principle

- Hederagenin, a triterpenoid saponin.
- All parts are toxic; poisoning occurs from eating the berries or other plant parts.

Signs

- Diarrhea and vomiting occur early.
- Followed by excitement, dyspnea.
- Fever may occur.
- "Convulsions", coma may occur.
- Death (rare).



English Ivy - Note the shiny 5-lobed leaves; the twining stems with root clusters for attachment; the flower, fruit, and seed (enlarged, lower right); and the star-shaped hairs (lower center) of this attractive plant.

Sesbania spp.

Sesbania drummondii - Drummond sesbania, poison bean, senna bean, rattlebox, rattlebush, coffee bean, sennie bean
S. punicea - Coffee bean, purple rattlebox, daubentonia, brazil rattlebox
S. vesicaria - Bagpod sesbania, bladderpod, coffee bean

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Herbivores, fowl	Hours to days	Days to week, potentially lethal	

Familly - Leguminosae (pulse or bean family)

Description

- *S. drummondii*:
    - Plant - Perennial shrub or small tree.
    - Leaves - Alternate, pinnately compound; leaflets are oblong, narrow, and 1/2 - 1 inch long.
    - Flowers - Yellow, showy, slender (1/2 inch across), in loose racemes.
    - Fruit - Legume pod, oblong, compressed longitudinally, 4-winged 2.5 - 3.5 inches long, seeds are separated by transverse partitions.
- *S. punicea:*
    - Plant - Perennial shrub or tree up to 12 feet tall.
    - Leaves - Alternate pinnately compound; leaflets which are oblong and 3/4 - 1 inch long.
    - Flowers - Showy, red, orange or scarlet (3/4 - 1 inch) dense racemes.
    - Fruit - Legume pod, oblong, compressed longitudinally, 4-winged, 2 - 3 inches long on a stalk up to 1/2 inch long.
- *S. vesicaria:*
    - Plant - Erect annual, often grows in clumps.
    - Stem - Bright green, erect, slender, woody, straight.

  - Leaves - Alternate, pinnately compound; leaflets number 20 - 52, are narrow, oblong, waxy green, 3/4 - 1.5 inches long and broad.
  - Flowers - Yellow or bright red, in long peduncled axillary racemes of 2 - 5.
  - Fruit - Legume pod, pendate, elliptical, wingless, somewhat compressed, 2 seeded.

Habitat

- *S. drummondii* - Coastal plain from Florida to Texas; Mexico. Previously cultivated fields; sandy soils; seasonally wet, waste places; often found growing in shallow water.
- *S. punicea* - Northern Florida to Louisiana; cultivated in Florida; introduced from Mexico. Ornamental introduced into USA and now naturalized on ditch banks, fence rows and waste places.
- *S. vesicaria* - Coastal plains from North Carolina and Florida to Texas. Rich soils; damp soils along streams; old fields; overgrazed pastures; disturbed waste places.

Toxic Principle

- Saponins are believed to be the primary toxic constituents.
- Primary gastrointestinal damage results with possible hemolysis if enough saponin absorbed.

Susceptible Species

Fowl, sheep, cattle and goats.

Toxicity

- General:
  - Seeds retain toxicity for a number of years.
  - Irritates the GI tract, allowing more rapid absorption of plant constituents.
  - Green seeds are more toxic than mature seeds, but both are toxic.
- *S. vesicaria*
  - Fowl:
    - One hundred seeds are toxic and 150 may be lethal.
    - 1.13 - 2.0% of BW of seeds caused rapid death.
    - Seeds fed at a rate of 5 - 20 per day caused death in 2 - 7 weeks.
    - Two hundred seeds fed at one time caused death in 1 week.
    - Two percent of BW of leaflets caused no overt toxicity.
  - Sheep:
    - Minimum lethal dose of seeds in 0.05% of BW
    - signs occur by 24 hours and death in 56 hours.
  - Cattle:
    - 0.15% of BW of seeds produced subacute toxicosis and death after 14 days.
    - Two percent of BW of seeds produced signs in 24 hours and death in 2 days.
    - Most cattle losses occur in fall and winter when the stem still carries the pods.
    - Cattle may develop craving for the seeds, but plants are usually distasteful.
- *S. drummondii*
  - Less than 2 oz of seeds may be lethal to large animals.
  - Leaves and pods are less toxic.
  - Sheep:
    - Approximately 1 oz of seed is a lethal dose.
    - 0.1% of BW is a minimum lethal dose.
    - 0.07% of BW caused clinical signs.
- *S. punicea:*
  - Fowl:
    - Nine seeds per bird was lethal to 3 of 5 hens.
    - 0.63% of BW of seeds caused 100% mortality to chicks.
  - Sheep:
    - 0.1% of BW of seeds caused fatalities.

Signs

- General:
    - Signs usually appear a day or so after consumption, up to 2 days.
- Fowl:
    - Prostration, diarrhea, light scaly comb when fed in smaller amounts, to dark (congested) combs when fed in large amounts.
- Sheep, Cattle:
    - Anorexia, depression, arched back, uneasiness, hemorrhagic diarrhea but sometimes constipation occurs.
    - Rapid, shallow breathing, fast, irregular pulse (shock).
    - Coma and death.

Lesions

- Fowl:
    - Necrotic enteritis and with less severe toxicosis, inflammation.
    - Necrosis of the gizzard.
    - Fatty degeneration of the liver.
- Sheep:
    - Gastroenteritis posterior to the rumen.
    - Degenerative changes in the gastric and mesenteric lymph nodes.
    - Liver and kidneys become congested and friable.
    - Dark, tarry blood with small thrombi.
    - Hemorrhage.
- Cattle:
    - Severe, hemorrhagic abomasitis and hemorrhagic enteritis in the small intestine.
    - Hepatic and renal degeneration, sometimes hepatic necrosis.
    - Sprouted seeds may be found in the rumen.

Diagnosis

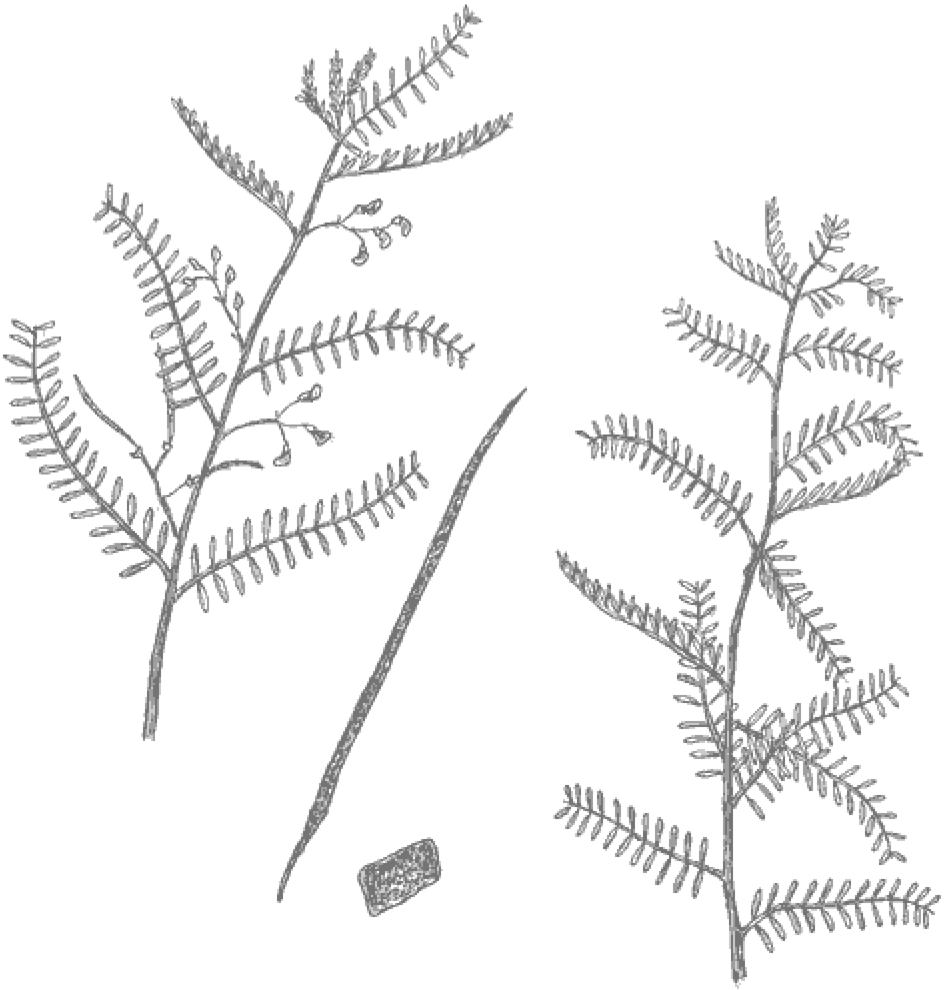
- Identification of *Sesbania*, evidence of consumption, especially of seed, appropriate clinical signs and lesions.

Treatment

See other *Saponaria* handout.

Prevention

Avoid contact with the plant and avoid seed year round. Remove and destroy developing pods from ornamental bushes. The herbicide 2,4-D may be used to control young plants. *S. vesicaria* may be mowed if abundant.



Hemp Sesbania. - Note the long, pinnately divided leaflets, the pea-shaped flowers, and the long slender pod and rectangular plump seed (enlarged, lower left) of this unusual legume.

Purgative Glycosides

Helleborus Niger - Christmas Rose

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants that Affect the Gastrointestinal Tract (Part I)
Most species	Hours	Days, poisoning is rare	

Common garden perennial considered poisonous by the major authors from Dioscorides to the twentieth century, but few documented cases of poisoning are on record, especially in this century.

Toxic Principle

Contains purgative glycosidic principles.

Signs

- May produce gastric distress and other effects in animals and human beings.
- Secondly nervous effects also may be observed.

Trichothecenes

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Trichothecene Mycotoxins: Deoxynivalenol, T-2 Toxin, Diacetoxyscirpenol [DAS] Macrocyclic Trichothecenes

(also see Dermal Effects of Trichothecenes)

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Trichothecenes
Deoxynivalenol (vomitoxin)	Swine, cattle, dogs, and poultry	Hours to days	Days; unlikely to be lethal	
T-2 toxin, HT-2 toxin, diacetoxysciprenol (DAS), related and macrocyclic trichothecenes	Cattle, swine, small animals, poultry	Hours to chronic	Days, potentially lethal	

Introduction

Trichothecene mycotoxins: (12,13 epoxytrichothecenes) comprise a group of over 50 compounds of widely varying toxicity that are produced primarily by field fungi of the genus *Fusarium*.

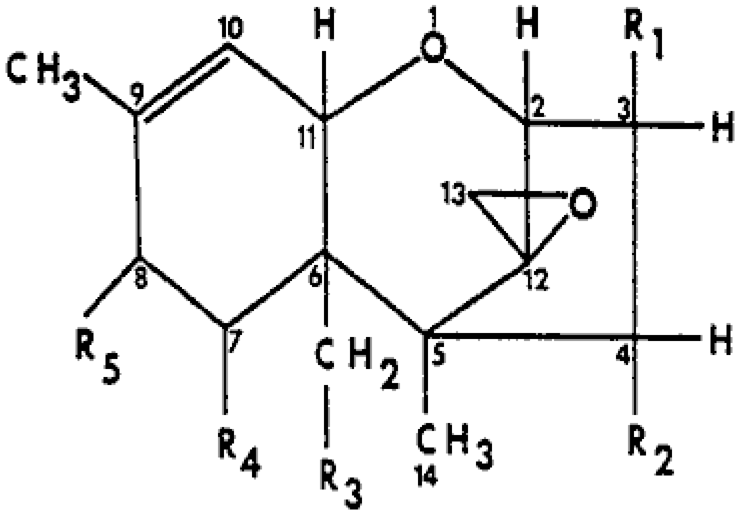
Sources

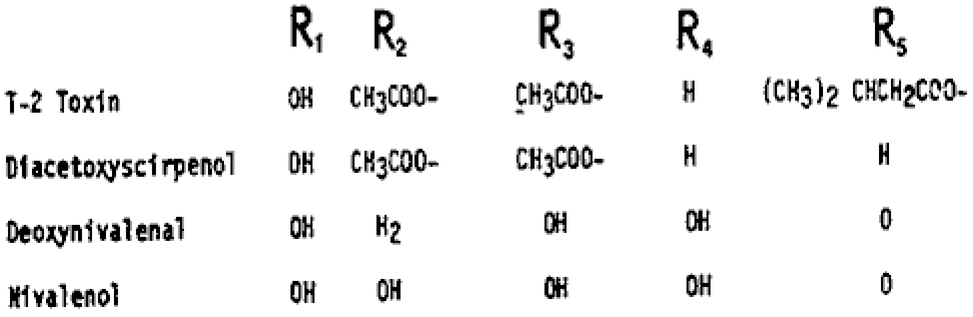
- Trichothecenes tend to be produced in toxic concentrations in years of wet weather when harvests are delayed and prolonged.
- Trichothecenes known to cause problems in farm animals include: deoxynivalenol (vomitoxin), nivalenol, T-2 toxin, diacetoxyscirpenol (DAS), macrocyclic trichothecenes (roridin A verrucarin A satratoxins), as well as others. In the U.S. and Canada, deoxynivalenol appears to be the most significant member of the group despite its comparatively low toxicity. T-2 toxin has caused widespread epidemics in human beings in the Soviet Union and, as with DAS, is an occasional cause of outbreaks of important toxicoses in animals in North America.
- Deoxynivalenol is produced by *Fusarium* fungi, especially *F. roseum* (*Giberella zeae*, *F. graminearium*) with corn (*Zea mays*) and sometimes wheat (*Triticum* spp.) as well as other small grains being the most important sources of exposure to livestock.
    - Mild temperatures tend to encourage mold growth and cool temperatures increase toxin production by *F. roseum*. Therefore fluctuating warm to cool temperatures in the presence of high grain moisture concentrations increase the likelihood of deoxynivalenol and zearalenone poisoning. These toxins arise especially as a result of field infection, but occasionally improper storage can greatly magnify the problems.
- T-2 toxin is produced especially by *F. sporotrichioides*.
- Undulating temperatures on the cold side tend to be associated with contamination of cereal grains with T-2 toxin and diacetoxyscirpenol. Thus, T-2 toxin and diacetoxyscirpenol occur especially during years of delayed harvests when grains are left in the field over the winter and temperatures are highly fluctuant. These toxins, along with deoxynivalenol and zearalenone, were detected in specimens of the alleged chemical warfare agent, yellow rain. T-2 toxin may occur in corn but the highest concentrations generally occur in small grains such as barley and wheat. Forages are sometimes contaminated.
- Macrocyclic trichothecene toxins in plant tissues of the *Baccharis* genus cause severe toxicoses in herbivores in Brazil.
- Macrocyclics also are sometimes produced by *Stachybotrys atra* in wet forages and/or straw as well as in rain-damaged building materials and water-soaked air ducts. All these sources have resulted in clinical poisoning problems.

Mechanisms of Action

- Trichothecenes are potent inhibitors of peptidyl transferase a ribosomal enzyme that is essential for protein synthesis. Thus, the trichothecenes inhibit protein synthesis.
- Trichothecenes also inhibit uptake of amino acids.
- Trichothecenes promote uptake of calcium and this is believed to trigger apoptosis.

Some Trichothecene Mycotoxins





	R_1	R_2	R_3	R_4	R_5
T-2 Toxin	OH	CH_3COO-	CH_3COO-	H	$(CH_3)_2$ $CHCH_2COO$-
Diacetoxyscirpenol	OH	CH_3COO-	CH_3COO-	H	H
Deoxynivalenal	OH	H_2	OH	OH	O
Nivalenol	OH	OH	OH	OH	O

Toxicity

- Experimentally, 4 ppm deoxynivalenol has caused a 2% reduction in feed intake while at 40 ppm a 90% reduction was observed. In the field, however, concentrations of DON associated with feed refusal may be as low as 1 ppm.
- T-2 Toxin and DAS are far more acutely toxic than deoxynivalenol, T-2 and DAS infrequently cause major outbreaks of serious toxicosis in livestock and poultry.

Signs

- Deoxynivalenol (DON, Vomitoxin):
    - Swine appear to be most susceptible, but cattle, horses, dogs and poultry are all reported to be susceptible.
    - Though not among the more acutely toxic trichothecenes, deoxynivalenol, has caused great economic loss to the livestock industry.
    - The predominant sign associated with contaminated feed is reduced feed intake (or occasionally feed refusal) and decreased rate of gain.
    - Other signs may include soft stools, diarrhea, failure to thrive, and a predisposition to other disease entities and poor nutrition.
    - Vomiting is infrequently seen therefore the name vomitoxin seems inappropriate.
    - Animals may develop a resistance to deoxynivalenol and make compensatory gains.

    - Although a mild thickening of the squamous mucosa of the stomach has been noted experimentally, specific lesions may not be found.
- T-2 Toxin, Diacetoxyscirpenol (DAS), and Macrocyclic Trichothecenes.
    - Problems involving T-2 toxin, DAS, and macrocyclic trichothecenes occur mainly in cattle, hogs and poultry, and occasionally in horses, dogs, cats, and humans.
    - Signs most often would include:
        - Increased incidence of infection.
        - Reduced feed intake or feed refusal.
        - Vomiting and diarrhea.
        - Necrosis of skin and oral mucosal damage.
    - Less often one may see:
        - Hemorrhage and necrosis of GI mucosa (high doses).
        - Destruction of hemopoietic tissue and lymphoid necrosis (high doses).
        - Meningeal hemorrhage (massive doses).
        - Shock and death (massive doses).

Reproductive Effects

- At doses toxic to the dam, embryo toxicity and fetotoxicity, and possible abortion may occur.
- Testicular damage in males may occur with highly toxic levels of exposure.
- *Stachybotrys atia*, cause of stachbotryotoxicosis is a black mold that produces macrocyclic trichothecenes. These toxins in straw have poisoned horses and farm workers. When the mold grows in water-damaged homes or air ducts people become chronically affected.

Dermal Effects of Trichothecene Mycotoxins

- Only the more potent trichothecene mycotoxins are known for their effects on the skin. The local cytotoxic effects of these compounds may produce lesions on the snout, muzzle, lips and tongue. T-2 toxin, diacetoxyscirpenol and other trichothecenes, especially the macrocyclic toxins which have been recognized primarily in Europe, have dermal effects although other effects are more toxicologically important. The trichothecene believed to be of greatest importance in the USA, deoxynivalenol, also called vomitoxin, is less potent in most respects and is not known for any significant dermal effects.
- Stachbotryotoxicosis results from macrocyclic trichothecenes in Europe, especially in the eastern countries. The most severe outbreaks have occurred in large animals and are a result of contact with contaminated forages. Persons handling the affected forages have also experienced dermal and respiratory irritation. Affected animals experience the effects of the cytotoxic properties of the trichothecenes present. Perioral, pharyngeal and gastrointestinal irritation all result.
- Similar perioral, pharyngeal and gastrointestinal effects are seen with T-2 toxin and diacetoxyscirpenol.
- In calves dosed with T-2 toxin orally for up to 6 weeks, atrophy of the thymus was a consistent finding. Clotting disorders and reproductive problems have also been reported with T-2 toxin but the former have not been readily reproduced experimentally.

Diagnosis

- When a history includes feed refusal and failure to thrive, several mycotoxins should be included in the differential diagnosis.
- When mycotoxins are suspected, feed should be submitted for a mycotoxin screen.
- It may be wisest to submit some of the worst looking feed to account for "the worst case exposure" and a separate sample collected as to represent the balance of the feed on hand (a composite from several locations) to represent the feed as a whole. Ship at least 3 kg of each frozen or at a moisture concentration of 3% or less to the lab via priority mail or some even faster method.
- Testing for the presence of the trichothecene mycotoxins in feed is the most important means of arriving at a definitive diagnosis. Specific quantitative assays are available for a limited number of trichothecenes at most diagnostic laboratories. However, for the most comprehensive screen for trichothecenes, contact Dr. Howard Casper at the Toxicology Laboratory at North Dakota State University in Fargo, ND (telephone: 701/231-7529). Agri-Screen ELISA tests for DON and T-2 toxin are available.
- These mycotoxins are not found at very high concentrations in tissues, although stomach contents may contain detectable levels if the animals were eating prior to death.

Treatment

- There are no specific antidotes for trichothecene mycotoxins, therefore, supportive and symptomatic treatment are indicated.
- Questionable feed should be removed and replaced by good quality feed with additional protein supplementation.
- Stress should be reduced to a minimum.

Prevention

- These mycotoxicoses are best controlled by proper grain handling and avoidance of questionable feeds.
- When necessary, analyses may be performed on feed, however, a negative test result does not preclude the presence of mycotoxins in some other areas of the bulk feed.
- Test animals can also be fed suspected grain and monitored for feed refusal and other signs of trichothecene mycotoxicoses.

Other Mycotoxins, Bacterial Toxins, Zootoxins, and a Yet-To-Be Identified Agent that Affect the Gastrointestinal Tract

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Garbage Toxicoses - Carrion Toxicoses - Bacterial Food Poisoning

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Other Mycotoxins, Bacterial Toxins, Zootoxins, and a Yet-To-Be Identified Agent that Affect the Gastrointestinal Tract
Bacterial toxins (food poisoning; most garbage poisonings, most carrion toxicoses; bacteria-contaminated Christmas tree water)	Small animals	Minutes to hours	Days; very often lethal	
Endotoxins and enterotoxins	All species	Minutes to hours	Days; often lethal	
Staphylococcal enterotoxins	All species	Minutes to hours	Days; often lethal	
Clostridial enterotoxins	Most species	Hours to days	Days; often lethal	

Sources

- Waste food materials or dead animals contaminated with bacteria, bacterial toxins and sometimes other toxicants.
- Protein-rich garbage serves as a favorable substrate for the growth of microorganisms and the production of toxins.
- Palatable foreign refuse is often present, such as meat wrappers (especially strings) and other substances which can serve as foreign bodies.
- Problems are more common in warm seasons and regions, especially when less than desirable hygienic practices or roaming are permitted.
- Food considered unfit for human consumption but fed to the family dog is another source.
- High moisture dog food, left at a warm temperature for a sufficient time is another common cause.
- **Note**:
  - Botulism, one form of occasionally encountered food/garbage poisoning intoxication is discussed under Toxicants Causing Paralysis.
  - Discarded foods from the refrigerator can also be a source of fungal toxins (see handout on Tremorgenic Mycotoxins).
  - The primary problem arising from bone ingestion is the formation of "bone-stools" which comprise a concretion that causes a terminal obstruction of the rectum and constipation.

Toxic Principles, their Mechanisms of Action, and Associated Signs

- Enterotoxins.
  - Common enterotoxin producing bacteria associated with enterotoxicosis in domestic animals include *Streptococcus* spp., *Salmonella* spp., and *Bacillus* spp.
  - Enterotoxins are proteinaceous substances that produce their biological effects by sorption with the gastrointestinal epithelium.
  - Enterotoxins are strong irritants of the gastric epithelial cells and therefore act as comparatively potent emetics.
  - The enterotoxins also disturb the permeability of the gastrointestinal epithelial cells, causing fluid and electrolyte losses into the lumen and interfering with the normal absorptive mechanisms of the gut.

  - Resolution of the dysfunction occurs primarily by necrobiosis of the affected cells and replacement with new cells migrating from the crypts, a process which takes 3 - 5 days. In the interim, the intestinal erosion may result in hemorrhage into the intestinal tract.
  - Initial irritation of the gastrointestinal tract may result in increased motility followed in 10 - 72 hours by dilation and stasis of the gut.
- Signs of Enterotoxicosis.
  - The first and often the only clinical sign of enterotoxicosis is vomiting, which generally begins within 15 - 180 minutes of exposure.
  - Often, this process removes sufficient toxin to give complete remission of clinical signs. Because of the irritating properties of enterotoxins, however, vomiting and retching may persist, eventually requiring medical intervention.
  - Diarrhea, often bloody may be observed 2 - 48 hours after exposure.
  - Anterior abdominal pain, which is often present initially, may in a period of hours extend over the rest of the cavity.
  - Stasis and dilation of the gut often follows with gas accumulation in the gut lumen, distention and accompanying pain.
  - In addition, the stasis favors the growth (or decreased removal) of gram negative bacteria, which liberate endotoxins (discussed below).
  - Often patients with stasis of the gut become critically ill and somewhat refractory to treatment.
- Endotoxins.
  - Gram negative bacteria in garbage, offal and other decaying animal tissues can serve as a potent source of endotoxins.
  - Endotoxins are lipopolysaccharide components of the cell walls of gram negative bacteria liberated upon bacteriolysis (lysis of the bacterial cells) before or after the ingestion of the offending substrate.
  - Absorbed by the gastrointestinal epithelium and act through a number of mechanisms including: **1**) activation of certain inflammatory mediators, such as proteases and other enzymes necessary for the activation of autocoids (histamines, kinins), **2**) cardiovascular insult and shock associated with release of catecholamines, thromboxane and prostacyclin as well as secondary pooling of blood in capillary beds with resultant hypoperfusion, anaerobic metabolism and lactic acidosis, **3**) alteration of the permeability of the gastrointestinal tract with loss of fluid into the lumen, **4**) interference with gut and other endocrine metabolism including those which influence gastric emptying, **5**) causing activation of pancreatic zymogens (may be an indirect result of pancreatic ischemia as a result of a drop in cardiac output during shock, rather than a direct effect) with secondary pancreatic autodigestion and acute pancreatitis, **6**) competition with insulin for the same receptor, **7**) activation of cascade reactions which activate complement and which initiate the clotting cascade, and **8**) uncoupling of oxidative phosphorylation in the myocardium is reportedly produced which may contribute to a negative inotropic effect.
  - The autocoids alter capillary permeability and increase hepatic portal resistance to blood flow with splanchnic pooling of blood.
  - The activation of clotting factors can result in disseminated intravascular coagulation.
  - Erosions of the epithelium may occur with frank hemorrhage into the lumen.
  - The net effect is one of profound circulatory shock, collapse and frequently death.
- Signs of Endotoxemia.
  - Fever, shivering.
  - Vomiting, diarrhea, abdominal pain and tenderness.
  - Abdominal distension.
  - Semiconsciousness.
  - Shock, often with muddy mucous membranes.
  - Often there will be gaseous gastrointestinal tract contents.
  - Often the offending material may be present in the vomitus.
  - Often the feces will be exceedingly foul smelling.
  - Watery or bloody diarrhea may be seen.

Diagnosis

- Attempts to differentiate **Enterotoxin** induced disease from **Endotoxin** induced disease are generally impractical and do not greatly influence the choice of therapeutic approaches.
- Diagnoses are based upon an appropriate history of exposure with the typical clinical signs, especially gastrointestinal upset, with gas, foul smelling vomitus or diarrhea, abdominal pain and subsequent

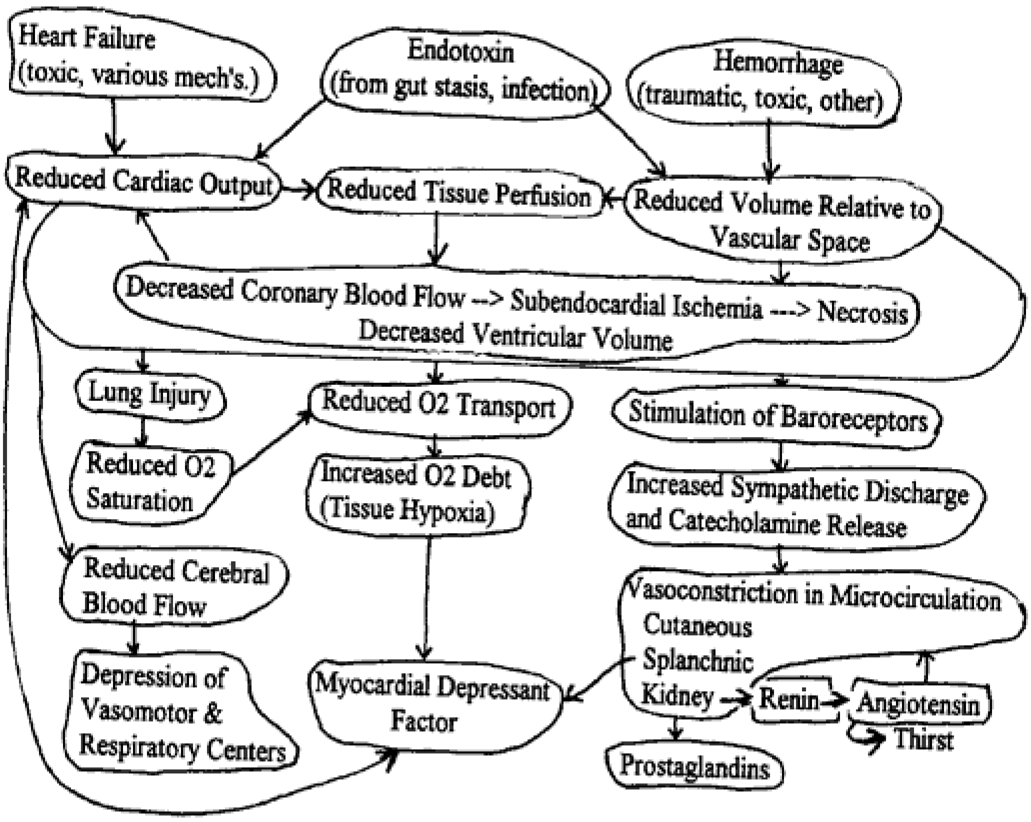
shock, and the associated increase in capillary refill time. The heart rate becomes rapid and the pulse has been described as thready.
- Radiographs (+/- barium) are indicated to rule out foreign bodies and intestinal displacement, including volvulus, torsion or intussusception.
- Rule out acute pancreatitis from other causes.
- Rule out acute hepatic or renal failure.
- With endotoxemia, a transient leukopenia, usually with a neutropenia followed by an increase in the leukocyte count with a predominance of polymorphonuclear granulocytes is observed.
- Fever is typical of endotoxemia, followed by hypothermia as the shock state progresses.
- The liver may be engorged and the resultant enlargement may make it palpable.
- Monitoring of blood glucose may be used to detect early endotoxic shock. In endotoxemia inhibition of gluconeogenesis by endotoxins, depletion of hepatic glycogen, and increased peripheral use of glucose may result in hypoglycemia.

Treatment

- Treatment is also not greatly influenced by the differentiation of Enterotoxin vs. Endotoxin diagnosis.
- Goals of therapy include:
  - Limit absorption of the offending material.
  - Combat fluid and electrolyte imbalance.
  - Combat shock and secondary pancreatic hypoperfusion.
  - Control bacterial proliferation to prevent septicemia.
- Specific approaches may include:
  - The use of emetics for animals very recently exposed and who have no contraindications present such as severe weakness or semiconsciousness, as well as others.
  - The use of gastric or enterogastric lavage if large amounts of toxic materials are present (usually not necessary due to pronounced emesis and initial gastrointestinal motility: but may be of value if early stasis has ensued.
  - The vigorous use of activated charcoal administration.
  - The appropriate use of fluid and electrolyte therapy, as well as bicarbonate if indicated for metabolic acidosis.
  - Systemic parenteral chloramphenicol. Note the aminoglycosides are generally regarded as contraindicated because they may synergize with the endotoxins present in depressing the myocardium.
  - Heparin may be of value in very early instances of disseminated intravascular coagulation.
  - Corticosteroids may be life-saving in cases of severe circulatory shock.
  - Glucose solutions may be of benefit in promoting urinary output, while acting as a limited source of calories.
  - Supportive care may be needed for days after an episode of garbage toxicosis to prevent dehydration, electrolyte imbalance and secondary infection.
  - A frequently provided bland diet may be of benefit.
  - Some practitioners favor the use of cultured yogurt as a means of providing a "beneficial" flora.
  - Flunixin (Banamine) useful for its antiprostaglandin effects and possible direct antiendotoxin effects. To be effective must be given early in endotoxemic shock.

Note - Practitioners have long associated pancreatitis and malabsorption syndromes with repeated episodes of garbage toxicosis. Such repeated episodes must therefore be avoided.

Shock
Primary Mechanisms


Heart Failure (toxic, various mech's.)
Endotoxin (from gut stasis, infection)
Hemorrhage (traumatic, toxic, other)
Reduced Cardiac Output
Reduced Tissue Perfusion
Reduced Volume Relative to Vascular Space
Decreased Coronary Blood Flow --> Subendocardial Ischemia ---> Necrosis
Decreased Ventricular Volume
Lung Injury
Reduced O2 Saturation
Reduced O2 Transport
Increased O2 Debt (Tissue Hypoxia)
Stimulation of Baroreceptors
Increased Sympathetic Discharge and Catecholamine Release
Reduced Cerebral Blood Flow
Depression of Vasomotor & Respiratory Centers
Myocardial Depressant Factor
Vasoconstriction in Microcirculation
Cutaneous
Splanchnic
Kidney
Renin
Angiotensin
Thirst
Prostaglandins

Antibiotic-Induced Enterocolitis In the Horse, Guinea Pig, and Rabbit

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Other Mycotoxins, Bacterial Toxins, Zootoxins, and a Yet-To-Be Identified Agent that Affect the Gastrointestinal Tract
Horses, rabbits, guinea pigs, other posterior fermenters	Hours to days	Days; very often lethal	

Sources

- Antibiotic contamination from feed mill - usually after mixing a batch of medicated feed for swine or cattle.
- Access to swine or bovine medicated feed.
- Use of wrong oral antibiotic in the horse, guinea pig or rabbit.
- Hamsters may also be susceptible.

Toxicity

- "Toxic" antibiotics in horse, guinea pig, and rabbit.
    - Lincomycin at 0.5 mg/kg BID.
    - Tetracycline.
    - Tylosin.
    - Neomycin.
    - Penicillin, oxytetracycline, streptomycin, and erythromycin have been implicated in the syndrome in guinea pig (chloramphenicol 30 - 60 mg/kg can be used)

    - Penicillin, ampicillin, vancomycin, erythromycin, cephalosporin, lincomycin, and gentamicin have been implicated in toxicity in hamster (chloramphenicol 50 mg/kg antibiotic of choice).

Mechanism of Action

The regular gut flora are killed and species of *Clostridium* bacteria overgrow with increased enterotoxin production. *Clostridium difficile* is among the most important toxigenic species. It produces two toxins that alter the intracellular protein known as "rho" to cause disorganization of the cytoskeleton of enterocytes.

Signs

- Anorexia.
- Nonresponsiveness and lethargy.
- Profuse diarrhea.
- Muddy mucous membranes.
- Tachycardia, dyspnea, and colic possible.
- Death.

Lesions

Acute catarrhal to hemorrhagic typhlitis and colitis; gastrointestinal mucous membranes very edematous.

Diagnosis

- Culture feces.
- Test feed for antibiotics.
- Differential.
    - Salmonella, Colitis-X.

Treatment

- Fluids and bicarbonate.
- Potassium added to fluids (slowly) as needed (monitor serum concentration).
- Activated charcoal.
- Flunixin meglumine.
- Normal gut flora.
- Antibiotics not secreted into gut.
- In preliminary studies, bacitracin has been shown to be useful in treatment and prevention of antibiotic-induced colitis in horses. Its use is not yet recommended in clinical practice.
- Steroids.
- An anecdotal report suggests that metronidazole plus yogurt (as a source of *Lactobacillus* organisms) is effective for antibiotic-treated rabbits experiencing significant gastrointestinal problems. The drug has reported activity against *Clostridia* and may therefore be a rational therapy.

Section XIII: Toxicants that May Affect the Oro-Pharyngeal and Gastrointestinal Tract

Chemical Agents Including Mycotoxins

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Acids and Alkalis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Chemical Agents Including Mycotoxins
Corrosive alkalis	All species	Seconds to hours	Hours to days; potentially lethal	
Corrosive acids	All species	Seconds to hours	Hours to days; rarely lethal	

Sources

- Acids and alkalis are also sometimes referred to as caustics or corrosives. Other compounds, such as concentrated phenol, concentrated iodine and silver nitrate may also have a corrosive or caustic effect. Therefore the terms corrosive or caustic are not synonymous with acids or bases.
- The frequency of serious alkali ingestion is more common than serious acid ingestion.
- Alkalis include:
    - Sodium hypochlorite (Clorox and similar bleach solutions) - One of the more common agents ingested.
    - Lye, which is sodium or potassium hydroxide - One of the most common causes of serious toxicoses.
- Acids include:
    - Hydrochloric, sulfuric and (rarely) hydrofluoric acids. Muriatic acid is another name for hydrochloric acid. Naturally there are others, but they are less commonly encountered as toxicants by domestic animals.

Mechanisms of Action

- Alkalis.
    - Hyperthermic injury, documented following lye ingestion.
    - Saponification of fats (independent of hyperthermic effect).
    - Stricture formation secondary to esophageal ulceration is unlikely unless the pH reaches 12.5.
- Acids.
    - Desiccation (drying) and generation of heat.
    - Acids do not tend to penetrate as deeply as do bases, but they do cause coagulation necrosis.
- Location, frequency and severity of lesions depends upon:
    - Chemical properties of the particular compound.
    - Volume and concentration to which the animal is exposed.
    - Contact time with the tissues.
    - Presence of other ingesta in the gastrointestinal tract at the time of exposure.
    - Tonicity of the pyloric sphincter.

Toxicity

- Lye tends to penetrate deeply into tissues whereas sodium hypochlorite and acids do not.
- Severity of injury is proportional to the concentration and the volume of the toxic solution.
- Prolonged contact increases the probability of severe injury increasing the risk of perforation.
- A full stomach is less vulnerable to corrosive injury than is an empty one because of dilution of the caustic agent.

- Pylorospasm, which can be induced by the caustic agent, increases the risk of local gastric injury.
- Because dogs and cats lap up materials their exposure to caustics tends to be slower and less of a problem than in children who "drink" such materials in quantity.

Signs and Lesions

- Alkali.
    - Lye commonly injures the oropharynx and esophagus and may injure the stomach as well.
    - In human patients solid lye tends to lodge in the oropharynx or esophagus and tissue injury at the site of contact continues until perforation occurs unless the particles are removed by vomiting or passed into the stomach.
    - Also in humans, liquid lye often presents a different and even more serious problem than solid lye. Up to 3 times as many patients developed esophageal injury after ingesting liquid lye than those ingesting solid lye. Liquid lye seems to cause almost immediate damage and often injures the stomach as well as the esophagus.
    - The most common immediate complication of lye ingestion is an esophageal burn which occasionally goes on to result in perforation. Gastric perforation is unusual but it occurs more often in patients ingesting liquid lye.
    - In some patients, respiratory distress occurs secondary to soft tissue swellings of the larynx, epiglottis, vocal cords or as a result of tracheal aspiration.
    - The principle delayed complications are esophageal stricture and pyloric obstruction.
    - Few instances of sodium hypochlorite induced esophageal stricture are on record and, in at least some of these, the history of exposure is of questionable certainty.
- Acids.
    - In human patients, the stomach is most frequently injured from acid ingestion, and the pyloric antrum is the area most often affected.
    - Esophageal injury is comparatively infrequent, affecting 6 - 20% of patients (humans).
    - Acute complications may include gastric perforation, acute peritonitis and shock, requiring immediate surgical and medical intervention.
    - Delayed complications may include sloughing of the gastric mucosa, peritonitis, perforation and sepsis. In some animals a primary pyloric stenosis may emerge over weeks to months after ingestion.

Diagnosis

- A history of exposure and appropriate clinical signs are sufficient for a tentative, clinical diagnosis.
- If possible use pH paper to assess the pH of the toxicant in its original container. Commonly, pH papers with a range of 1 - 12 are available as are high range papers with a range of 12 - 14. Both should be used if they are available (obtain ahead of time or check with a local hospital emergency department).
- As with other toxicoses, it is important to determine the particular agent ingested, its concentration, the quantity ingested, the duration since ingestion, whether vomiting has occurred since that time and whether a diluent was given thereafter.
- Examinations of the oral, pharyngeal and esophageal mucosae are desirable. It is possible to have significant esophageal pathology in the absence of oral damage, but this would be the exception, rather than the rule.

Treatment

- The use of emesis and lavage are generally regarded as **contraindicated** in acid or alkali ingestions, because of the possibility of re-exposure of the damaged tissues of the esophagus, because of the risk of rupturing an already weakened stomach, and because of the possibility of aspiration.
- Activated charcoal and saline cathartics are not indicated for ingestions of acids or alkalis because: **1**) activated charcoal is a poor adsorbent for acids or alkalis, **2**) tissue injury occurs so fast that, by the time the animal reaches the facility and is administered the treatment, it would do no good and **3**) activated charcoal may limit the ability to characterize any damage endoscopically.
- Corticosteroids are suggested for caustic ingestions in which there has been circumferential mucosal damage in order to limit fibroplasia and thereby minimize stricture formation. In order to be of benefit, the corticosteroid should be given within 48 hours of exposure to the caustic agent. However, care must be taken in selecting patients for corticosteroids use. The drugs are contraindicated in the presence of perforation because of masking of clinical signs and the possibility of reducing the success of surgical

correction. Noncircumferential esophageal burns do not require steroid therapy. When used, the steroids are given for a period of several weeks.

- Although disputed by some authors, experimental evidence is in favor of the use of antibiotics when there is a history of perforation and prophylactically when steroids are given.
- Respiratory distress, although serious when it occurs, is very rarely encountered. If severe, endotracheal intubation should be used if the tube can be inserted without causing additional damage to the laryngeal area. If that cannot be avoided, tracheostomy may be required.
- Aspiration into the respiratory tract is also infrequent, but in view of the gastric contents and irritation which may be present, extreme care should be taken to avoid this effect.
- Monitoring blood gases and appropriate measures to alleviate respiratory or circulatory embarrassment leading to anoxia or shock may be of benefit in such patients. These may include artificial respiration, oxygen, and more often, fluids, bicarbonate, and corrective electrolyte solutions.
- An analgesic may be indicated to alleviate pain.
- Survey X-rays may be taken of the thorax and abdomen.
- The use of diluents, especially, milk and water, are often recommended for ingestion of acids or bases although some authors feel that such steps are at best of questionable benefit unless the patient is treated within minutes of exposure.
- Alkalis.
    - Diluents are used with 2 goals in mind: **1**) To remove solid alkali materials from the oropharyngeal and esophageal mucosae; and **2**) To dilute the caustic material and decrease the degree of tissue damage.
    - Acids, such as lemon juice, acetic acid or vinegar are **contraindicated** in alkali toxicoses, due to the resultant exothermic reaction and associated thermal injury to the mucosae.
    - For solid lye ingestions, the use of milk is preferred over water but if not immediately available water should be administered.
    - For liquid lye ingestions, the use of diluents is more controversial because of a study involving humans, in which such therapy was associated with subsequent vomiting. The author feared that the associated reexposure of the esophageal mucosa would be likely to increase the injury. In view of the relatively infrequent occurrence of esophageal perforation in poisoned dogs and cats, the use of a diluent may have a more favorable risk/benefit ratio in these species than in humans. Investigation of the prevalence of vomiting and secondary complications in animals ingesting liquid lye with and without the addition of a diluent are needed to make a definitive recommendations.
- Acids.
    - Diluents are not known to be of reliable benefit in acid ingestion and, again, there is concern as to the possible increased risk of vomiting. Nevertheless, some of the most commonly relied upon reference systems (e.g., *Poisindex*) for human toxicoses still recommend their use. The use of a diluent is therefore recommended for acid ingestions, especially if the ingestion has occurred minutes prior to presentation.
    - Antacids, especially bicarbonate, are potentially contraindicated due to the release of heat and in the case of bicarbonate, gas bubbles as well.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Chemical Agents Including Mycotoxins
Hypochlorites (concentrated forms)	Small animals	Seconds to hours	Days; rarely lethal	
Formaldehyde	Dogs	Minutes to hours	Hours to days; often lethal	
Phenolics (concentrated phenol or cresol)	(See Hepatotoxic Chemicals and Drugs)			
Cholinesterase inhibitors	(See Inhibitors of Cholinesterase)			
Moldly red clover (salframine)	(See Muscarinic Agonists)			

Trichothecene Mycotoxins	(See Toxicants that Affect the Gastrointestinal Tract)	

- Phenolics (See Coal Tar, etc. under Hepatotoxic Chemicals and Drugs)
- Formaldehyde
- Cholinesterase Inhibitors (See Inhibitors of Cholinesterase)
- Moldy Red Clover (Slaframine) (See Toxicants with Muscarinic Effects but No Nicotinic Effects)
- Trichothecenes (the more toxic members of the group can cause oral lesions) (See Toxicants that Affect the Gastrointestinal Tract)

Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin

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In addition to the plants causing irritation of the oral and gastrointestinal tissues by virtue of oxalate crystals and histamine releasing compounds (members of the Araceae), several other plants may be of importance in isolated cases.

Sequelae from Perforating Plants Include:

- Otitis.
- Lameness.
- Fistulous tracts.
- Abscessation.
- Stomatitis.
- Suppurative pleuritis.
- Conjunctivitis.
- Suppurative arthritis.
- Infections due to common soil organisms such as *Nocardia* and *Actinomyces*.

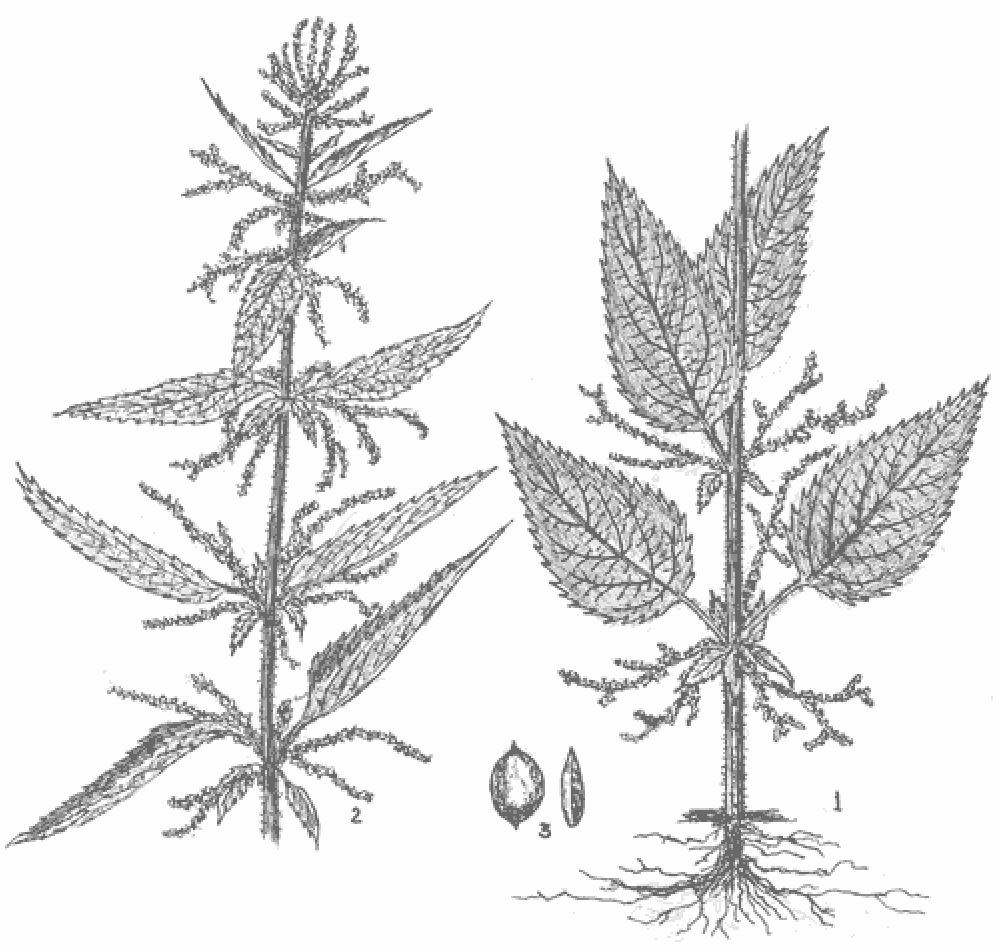
Nettles

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin
Nettles (*Urtica* and *Laportea*) (contain histamine)	Most species	Minutes to hours	Days; rarely lethal *	
Nettle spurge (*Cnidocolus*)	Most species	Minutes to hours	Days; rarely lethal *	
* Potentially lethal with secondary infection, such as after perforation of a foreign body				

- *Urtica* spp. and *Laportea* spp. as well as Nettle spurge (*Cnidocolus*).
- Primarily hunting dogs are affected.
- Abundant stinging hairs which contain varying amounts of acetyl choline, histamine, serotonin, formic acid and possibly other toxic constituents.
- The resultant clinical signs may include: Salivation, pawing at the mouth, emesis, respiratory distress, slow, irregular heart rate, muscle weakness, and occasionally death.
- Depending upon the clinical signs, atropine, antihistamines and supportive measures may be indicated.

Nettle Family

Urticaceae



Stinging Nettle, *Urtica dioica* L.

Perennial - Reproducing by seeds and underground rootstocks.
Stem - 2 to 7 feet (0.6 to 2 m) tall, slightly branched near the top, slender, rigid, covered with numerous stinging hairs.
Leaves - Dark green, coarse, opposite, 3 to 6 inches (7.5 to 15 cm) long, pointed with saw-toothed margins, sometimes rounded at base, covered with stinging hairs.
Flowers - Are greenish without petals and produced in clusters in the leaf axils. Male and female flowers borne separately but on the same plant.
Seed pod - 1-seeded.
Seeds - Small, egg-shaped, slightly rough, yellow to grayish-tan.
Found - In barnyards, fence rows, thickets, waste places, and roadsides; generally in damp rich soil. When this plant comes in contact with the skin it causes welts or inflammation.

Burdock

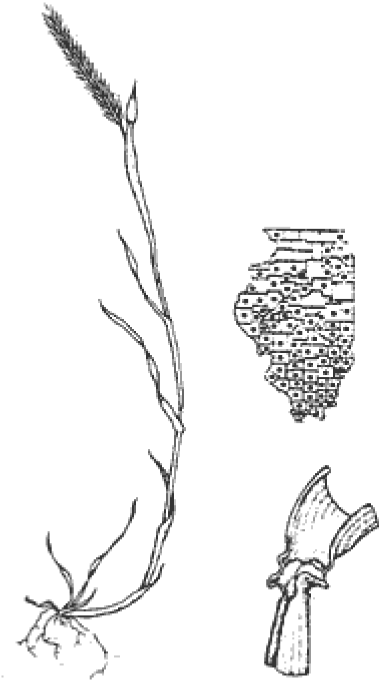
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin
Most species	Minutes to hours	Days; rarely lethal *	
* Potentially lethal with secondary infection, such as after perforation of a foreign body			

- *Arctium lappa*.
- Small hooks on flowers catch in hair of animals, especially dogs. Grooming imbeds these in the tongue and mouth which allows them to serve as a nidus for infection often resulting in a granular appearing glossitis and stomatis.
- Treatment is comprised of scraping these areas free of the plant material with a scalpel blade.

Wild Barley

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin
Wild Barley (*Hordeum*)	Most species	Minutes to hours	Days; rarely lethal *	
Bromes (*Bromus*)	Most species	Minutes to hours	Days; rarely lethal *	
* Potentially lethal with secondary infection, such as after perforation of a foreign body				

- (*Hordeum* spp.) and Bromes (*Bromus* spp.).
- Florets imbed and result in fistulous tracts in the skin.



Little Wild Barley (*Hordeum pusillum* Nutt) - Native, weedy, annual grass. It is a cool-season, short-lived species that attains a height up to 30 cm or more. It flowers and produces fruit during Spring and early Summer.
Flowers - The spikes are up to 6 - 8 cm in length and are dense and erect. Spikelets are 3 at each joint and are awned.
Leaves - The root system is shallow. The leaf blades are up to 7 cm long, flat, and somewhat rough on the upper surface.
Use or Importance - Limited grazing is about the only use made of this plant, and this occurs during Spring. The plant serves as an indicator of overgrazed prairie or pasture.
Habitat - it is most often found in disturbed areas within prairies. The species occupies a wide variety of soils. Found over much of the United States.

Sandburs

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin
Most species	Minutes to hours	Days; rarely lethal *	
* Potentially lethal with secondary infection, such as after perforation of a foreign body			

- *Cenchrus paucufloris*.
    - Cause irritation to legs and feet and may traumatize feet.

Other Plants Causing Trauma

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin
Goatheads (*Tribulus terrestris*)	Most species	Minutes to hours	Days; rarely lethal *	
Numerous cacti	Most species	Minutes to hours	Days; rarely lethal *	
* Potentially lethal with secondary infection, such as after perforation of a foreign body				

Other Plants Causing Trauma Include:

- Goatheads, *Tribulus terrestris*.
- Numerous cacti.

Plants of the Araceae Family (Plants Containing Oxalate Crystals and Histamine Releasers)

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Plants of the Araceae Family (Plants Containing Oxalate Crystals and Histamine Releasers)

***Dieffenbachia* spp.** - Dumbcane
***Philodendron* spp.** - *Philodendron* var. *cordatum*, horsehead, panela, red emerald, red princess
***Monstera* spp.** - Ceriman; also known as split-leaf *Philodendron* or *monstera*, mother-in-law, Swiss cheese plant, hurricane plant, fruit salad plant, cutleaf philodendron, Mexican breadfruit
Alocasia antiquorum* or *Colocasia - Elephant's ear
Zantedeschia aethiopica - Calla lily; arum lily
***Caladium* spp.** - Caladium, also called elephant's ear
Symplocarpus foetidus - Skunk cabbage
Calla palustris - Wild calla; water arum
***Xanthosoma* spp.** - Malanga, caladium, elephant's ear
***Epiprenum* (*Scindapsus*) spp.** - Devils ivy, golden pothos, marble queen, variegated philodendron, pathos, taro vine
Arisaema triphyllum - Jack in the pulpit
Arum maculatum - Cuckoo-Pint
Spathiphyllum clevelandii*, *Spathiphyllum floribundum*, *Spathiphyllum wallisii - Peace lily
Syngonium podophyllum - Arrowhead, syngonium

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Plants of the Araceae Family (Plants Containing Oxalate Crystals and Histamine Releasers)
Jack-in-the-pulpit (*Arisaema triphyllum*)	Most species	Minutes to hours	Days; potentially lethal; poisoning is rare	
Dumbcane (*Dieffenbachia*)	Dogs, cats	Minutes to hours	Days; potentially lethal	
Philodendron (*Philodendron* spp.)	Dogs, cats	Minutes to hours	Days; potentially lethal	
Elephant's ear (*Colocasia* spp.)	Dogs, cats	Minutes to hours	Days; potentially lethal	
Alocasia (*Alocasia* spp.)	Dogs, cats	Minutes to hours	Days; potentially lethal	
Split-leaf philodendron (*Monstera deliciosa*)	Dogs, cats	Minutes to hours	Days; potentially lethal	
Wild calla (*Calla*)	Most species	Minutes to hours	Days; potentially lethal	
Skunk cabbage (*Symplocarpus*)	Most species	Minutes to hours	Days; potentially lethal	
Arrowhead plant (*Syngonium*)	Most species	Minutes to hours	Days; potentially lethal	
Others	-	-	-	

Description

A number of ornamental plants in the Family Araceae produce similar toxic signs that will be discussed as a group. A large array of ornamental plants fit into this category.

Toxic Principle

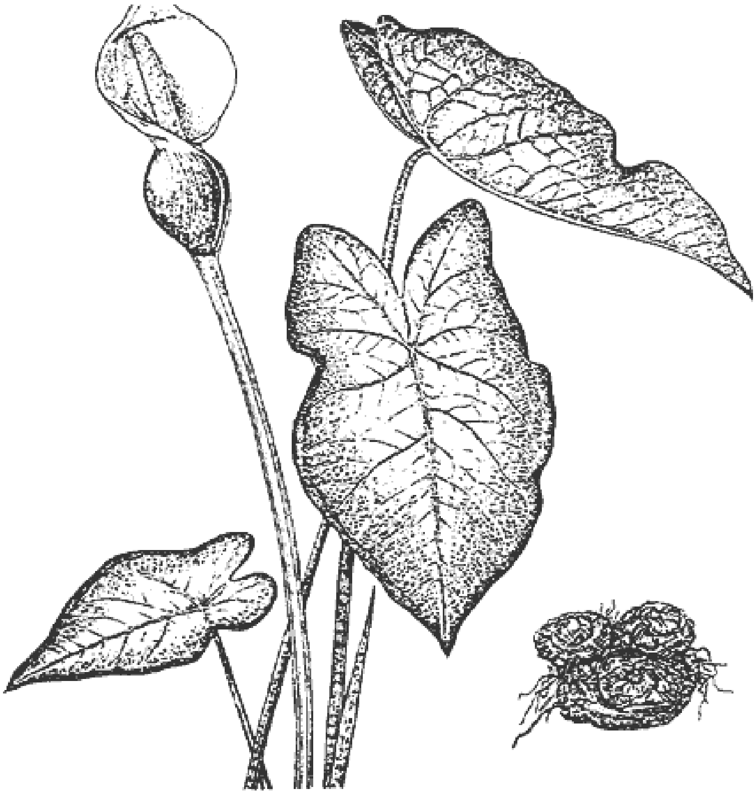
- All parts are usually poisonous, although the leaves may sometimes be devoid of toxin.
- Calcium oxalate crystals are felt to be one cause of the clinical signs. Recently toxicity has also been attributed to several proteolytic enzymes, which trigger the release of some potent kinins and histamines by the body. These kinins in turn cause several local reactions, which may be aggravated by the sharp calcium oxalate crystals contained in the plant tissues.
- Calcium oxalate crystals are thought to mechanically damage cells in the mouth during ingestion and may allow toxin to enter and create cellular havoc.
- It has been shown that dumbcane has specialized contractile cells that may actually propel the calcium oxalate crystal (rhabdites) into the tissue.

Signs

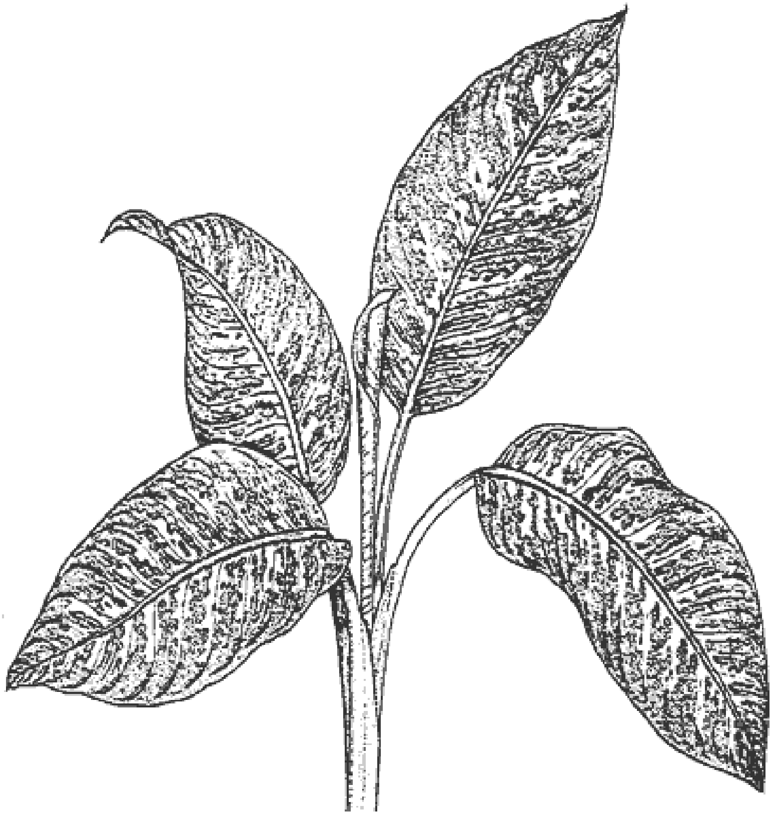
- Immediate evidence of pain and irritation upon chewing.
- Headshaking, intense salivation.
- Change in phonation.
- Swelling of the mucous membranes of the pharynx and tongue.
- Severe dyspnea may develop, but obstruction rarely develops.
- Nausea, vomiting, diarrhea, secondary dehydration, electrolyte imbalance and shock are possible.
- Very rarely - irregular heart beat, mydriasis, coma and death.

Treatment

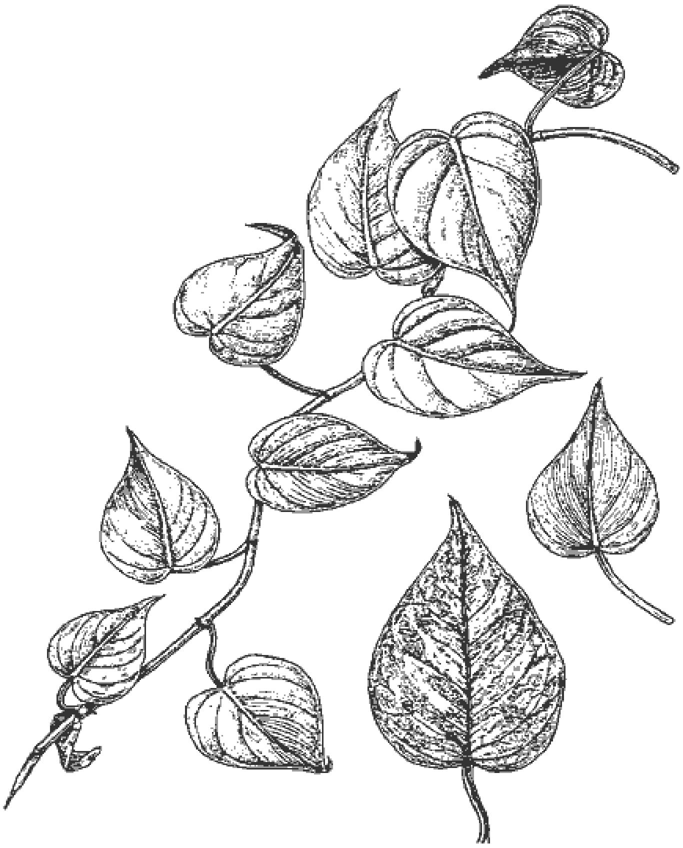
- Signs usually abate within 2 - 4 hours after treatment, but may persist for several days.
- Rinse mouth.
- Activated charcoal.
- Oral calcium (e.g., milk) may be helpful in precipitating any soluble oxalates.
- Antihistamines.
- Symptomatic and supportive care.
- IV fluids if vomiting or diarrhea are persistent causing dehydration or shock.



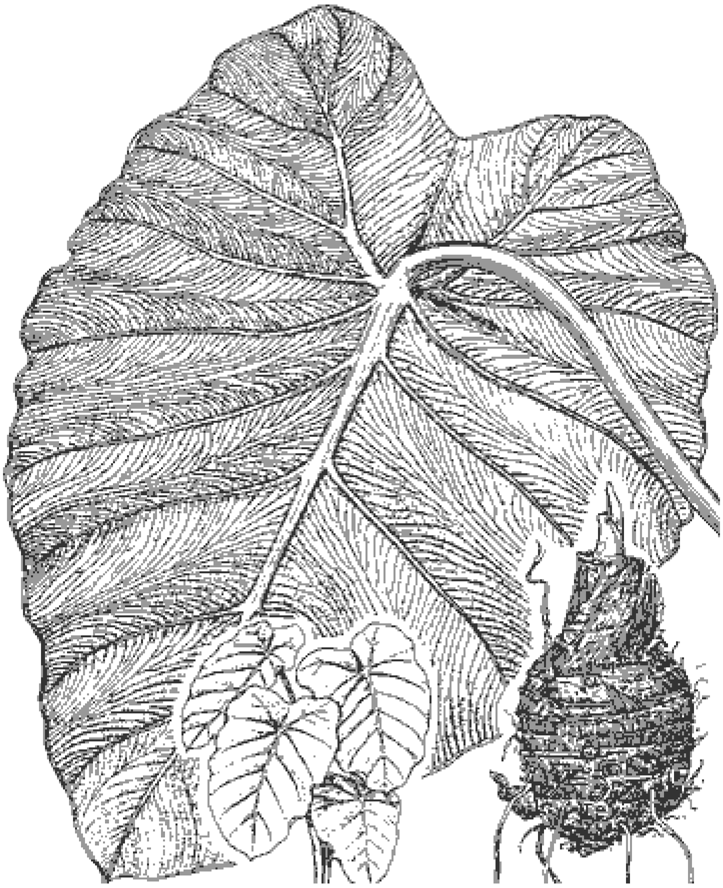
Caladium - The large heart shaped leaves, the flowers enclosed in a tubular bract (upper left), and the dormant tuber (lower right).



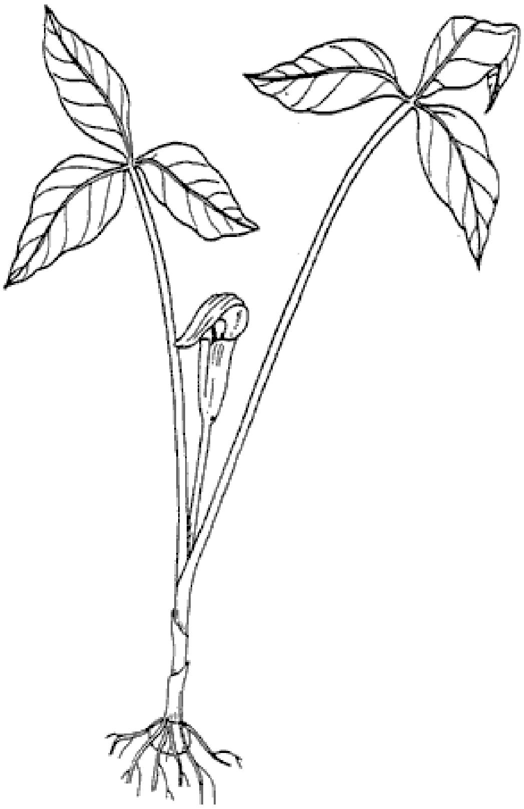
Dumbcane (*Dieffenbachia* sp.) - An ornamental with large variegated leaves that only rarely produces flowers or fruits.



Philodendron - The leaves of these trailing or climbing vines are heart-shaped, variously colored, and pointed. The leaf of pothos, a similar climbing vine commercially called philodendron, is shown below.



Elephant's Ear (*Colocasia*) - Note the large leaf, shaped like an elephant's ear, and the scaly tuber of this large ornamental plant.



Jack-in-the-Pulpit (*Arisaema triphyllum*).

Section XIV: Toxicants that Affect the Heart

Introduction to the Toxicology of the Cardiovascular System

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Introduction to the Toxicology of the Cardiovascular System

1. Principle Components and Functions of the Cardiovascular System

- Heart - Varies among vertebrate species with complete separation of the two sides of the heart (left and right) being present in birds and amphibians.
    - The right atrium accepts poorly oxygenated blood from the body. The right ventricle pumps blood into pulmonary artery on its way to the lungs. The oxygenated blood then enters the pulmonary vein which dumps into the left atrium. The left atrium pumps blood into the left ventricle which then pumps it into the aorta on its way to the systemic circulation (includes coronary arteries that supply the heart itself, the head, including the brain, and all the organs and tissues of the body.
    - The myocardium = the heart muscle, including the atrial and ventricular walls, and the papillary muscle.
    - The valves include the atrioventricular (right, left), pulmonary, and aortic.
    - Ion gradients (polarization) are established and maintained in the heart muscle and in specific nodes within the heart that help regulate the cardiac rhythm. The gradients (polarization) exist because Na^+ and Ca^{++} are pumped out of the myocardial cells (into the extracellular compartment) and K^+ pumped into the myocardial cells (intracellular compartment). Slow Ca^{++} flux is particularly important in the sinoatrial and the atrioventricular nodes. The ion gradients are achieved by the action of Na^+/K^+ ATPase (Na^+/K^+ pump), and by Ca^{++}-ATPase that pumps Ca^{++} out of the cells.
    - When the Na^+ channels open, Na^+ rushes in (causing temporary depolarization). The flow of electrons toward the more positive area of the cell (due to the charge associated with the sodium atoms) propagates the depolarization reaction along the membrane and other Na^+ channels open, continuing the process through the heart. Shortly after the entry of Na^+, K^+ begins to leave the myocardial cell via K^+ channels, thereby beginning the process of repolarization. The influx of Na^+, however, also triggers an influx of Ca^{++} as well as its release from intracellular storage sites (e.g. the sarcoplasmic reticulum). The increased free Ca^{++} in the myocardial cells increases coupling between the contractile actin and myosin fibers of the cell which results in shortening of myocardial fibers (myocardial cells are hooked together in fibers).
    - The usual pacemaker of the heart is the sinoatrial node, an area that depolarizes spontaneously and thereby initiates depolarization that progresses through the heart
    - The propagation of the impulse through the heart is normally facilitated by special conductile fibers in the heart (Purkinje fibers) and impeded by certain areas of slower conduction (such as between the atria and the ventricles) so that the heart "rhythmically squeezes the blood along" within the lumen, making it an extremely efficient pump
    - The electrocardiogram reflects the electrochemical activity in the heart that is associated with this sequence of depolarizations (which bring about systole = time of contraction) as well as repolarization events (occurs during diastole = time of relaxation; provides time for the heart to fill and the muscle to repolarize as it gets ready for the next depolarization event).
    - The movement of valves is largely passive (especially the aortic and pulmonary; similar to a parachute) as they prevent backward movement of the blood - one way flow.
    - The pulmonary circulation (and right heart) is low pressure, while the systemic circulation (and left heart) is high pressure. Volumes of flow in both sides are the same.
    - Birth defects that result in abnormal structure and disease states that alter the structure of valves or the overall size of the heart such that blood flow becomes more turbulent result in heart murmurs.
- Arteries
    - Aorta and major arteries - large tubes with considerable elastin.

    - Following contraction of the heart, and in conjunction with closure of the aortic and pulmonary valves, the aorta and pulmonary artery are distended by the influx of blood during systole, and the elasticity of the vessels maintains pressure in the system during diastole.
- Arterioles
    - Small "precapillary" vessels with muscular walls: contraction alternates so that various capillary beds take turns receiving blood over time. The arterioles thus conserve the overall volume of blood in the vasculature, thereby making less work for the pump.
    - Smooth muscle in the walls of arterioles and bronchi contract or relax in response to adrenergic agonists (epinephrine and norepinephrine).
        - e.g. vessels to the skin contract, coronary vessels and bronchi dilate
- Capillaries
    - The smallest porous blood vessels in the body; porous and allow extracellular fluid to leak into the tissues.
    - Site of delivery of water, electrolytes, oxygen, glucose, amino acids, fatty acids, and other nutrients, plus removal of waste products, carbon dioxide, excess acid, etc.
- Venules
    - Some muscle, but much less than the arterioles.
    - Help regulate pressure in capillaries.
- Veins
    - Carry poorly oxygenated blood back to the heart at greatly reduced pressure as compared to the arteries.
    - Some of the veins (e.g. in legs) contain valves to prevent backpressure or reverse flow
    - Vena cava
        - The anterior and posterior vena cavas come together as the oxygen depleted blood flows into the right atrium.
- Lymphatics
    - Extremely low pressure, one-way system flowing toward the heart.
    - Lymphatics pick up fluid that does not make it back into the capillaries and flow into larger lymphatics that coalesce into the thoracic duct.
    - The thoracic duct terminates where it empties into the vena cava.
- Endothelium
    - Cells that line blood vessels.
    - Metabolically active, produce and respond to a variety of hormones (e.g. prostaglandins).

2. Cardiovascular System Dysfunction

- Forms of cardiac dysfunction
    - Tachycardia = excessively rapid heart rates
    - Bradycardia = excessively slow heart rates
    - Arrhythmia = usually implies excessively irregular heart rhythm
        - Exception - Sinus arrhythmia is the normal variation in heart rhythm; controlled by the normal pacemaker of the heart (sinoatrial node).
        - Heart block - Termination of the conduction of the impulse through the heart; other areas usually take over as an alternate "pacemaker" of the heart.
        - Premature excitation (usually spontaneous discharges of electrochemical activity, often accompanied by contraction, lack of coordination with other aspects of the cardiac cycle may greatly diminish the efficiency of pumping), e.g. premature ventricular contractions.
        - Flutter - A rapid arrhythmia - atrial flutter is generally less serious than ventricular flutter.
        - Fibrillation - Irregular depolarizations with no more than "quivering of the heart" - ineffective pumping - often rapidly fatal - e.g. ventricular fibrillation.
    - Congestive heart failure (CHF)
        - Left heart failure - Back up of blood into the lungs, potential for pulmonary edema.
        - Right heart failure - Back up of blood into the systemic circulation, potential for accumulation of fluid in the abdominal cavity = ascites.
        - CHF may result from:
            - Interference with conduction of impulses through the heart (acute or chronic)
            - Lesions in the heart valves
            - Lesions in the myocardium
    - Cardiogenic shock

        - Shock is defined as acute peripheral circulatory failure due to derangement of circulatory control or loss of circulating fluid.
        - Cardiogenic shock is brought about by suddenly impeded pump failure: example, heart attack due to sudden occlusion of blood flow to the myocardium, or massive doses of cardiotoxic agents.
- Forms of vascular dysfunction
    - Excessive contraction of peripheral or cardiac arterioles (e.g. excessive doses of drugs that are derivatives of catecholamines).
    - Excessive relaxation of peripheral arterioles (e.g. due to a high dose of a drug that acts as a blocker of catecholamine receptors) - can lead to circulatory shock.
    - Increased permeability of capillary beds resulting in loss of fluid and insufficient blood volume for effective return of blood to the heart (e.g. bacterial endotoxins associated with some forms of food poisoning (e.g. *Escherichia coli*) or gut infections (e.g. *Salmonella*), or with a range of toxic substances (e.g. arsenic, antimony, several types of poisonous plants, high doses of heavy metals, etc.).

3. Drugs and Toxicants that Affect the Heart: Examples of Agents that Influence Excitability

- **Catecholamines**

    Cause formation of cyclic AMP in the heart that acts as a potent second messenger, triggering myocardial contraction in part through release of intracellular Ca^{++} stores.

- **Cocaine**
    - Mechanism of concern is inhibition of re-uptake of catecholamines.
    - Result is excessively stimulated myocardium, with severe tachyarrhythmias and often death.
- Verapamil

    Drug that blocks sodium channels, decreasing intracellular Ca^{++} concentrations, such that contractile activity decreases.

- **Cardiac glycosides** (e.g. digitalis)
    - Poisonous plant toxin and drug that inhibits Na^+/K^+ ATPase, such that intracellular sodium concentrations increase; Na^+ is exchanged for Ca^{++} (from outside the cell, as well as from intracellular depots in the sarcoplasmic reticulum and the mitochondria).
    - The excess intracellular free Ca^{++} increases coupling of actin and myosin, which at low doses can help congestive heart patients, but which at high doses can cause many types of cardiac arrhythmias resulting in CHF or cardiogenic shock.
- **Quinidine**

    An antiarrhythmic drug that inhibits Ca^{++} uptake by the sarcoplasmic reticulum.

- **Japanese Yew** (*Taxus*) (common ornamental plants; also wild species of yew)

    Alkaloids block electrochemical conduction through the heart.

- **Diethyl Ether and Halogenated Alkanes**
    - Examples include ether and chloroform (both formerly used widely as anesthetics), and fluorocarbons (e.g. trichlorofluoromethane, a constituent of Freons, used in refrigeration and air-conditioning equipment).
    - Effect = greatly exaggerated sensitivity of the heart to catecholamines - results in tachyarrhythmias.
    - Chronic exposure to certain haloalkanes has been associated with cardiomyopathies.
- **Examples of Agents that Cause Cardiomyopathy (degenerative or necrotic lesions in the muscle of the heart).**
    - Alcohol (ethanol) (cardiomegaly = enlarged heart, with lipid droplets in the myocardium), which may be complicated by acetaldehyde (metabolite of ethanol) effects, because acetaldehyde slows the heart at low concentrations and may increase the release of catecholamines at high doses.
    - Overdose with certain catecholamines, e.g. isoproterenol.

- Ionophore toxicoses.
- *Cassia* (poisonous plant) toxicoses.
- Allergic reactions associated with hypersensitive myocarditis.
    - Some penicillin reactions.
    - Some sulfonamide reactions.
    - Methyl-dopa induced cardiomyopathy.
- Cobalt (Co)
    - Acute high dose or chronic low dose exposure can cause cardiomyopathy in laboratory rodents and human beings.
    - Chronic Co toxicosis can cause vacuolation of Purkinje fibers and a slow heart rate.
- Lead (Pb)
    - Exposure *in utero* may pose the greatest risk.
    - Degenerative lesions and increased sensitivity to norepinephrine have been noted in the hearts of children exposed to high doses of lead.
- Antineoplastic drugs.
    - Doxorubicin.
    - Daunorubicin.
    - These drugs cause production of oxygen free radicals.
    - Lesions in human beings or laboratory animals include enlargement of the heart (dilation), atrophy and degeneration of the cardiac myofibers, edema, and fibrosis.

4. Drugs and Toxicants That Affect the Blood Vessels: Examples

- **Lead**

    Causes changes in elasticity of blood vessels by affecting the vascular ground substance. May cause sclerosis of renal vessels. Has caused hypertension in poisoned birds (pigeons).

- **Cadmium** (Cd)

    Increases synthesis of angiotensinogen, a precursor to angiotensin.

- **Estrogen-containing oral contraceptives**

    Increases synthesis of angiotensinogen, a precursor to angiotensin.

- **Ergot alkaloids**
    - Stimulate catecholamine receptors in peripheral vessels .
    - Result in gangrene and loss of extremities (fingers, toes, hooves, tails).

5. Drugs and Toxicants That Affect the Blood Volume: Examples

- **Diuretics**
    - Stimulate urine flow - Decreased blood volume and may alter electrolyte concentrations.
- **Agents that cause renal failure and severe fluid loss due to the combined effects of the inability to concentrate urine and sometimes vomiting (may be confused with vasoactive agents).**
    - Excessive doses of nonsteroidal anti-inflammatory drugs.
    - Excessive doses of sulfonamides.
    - Gentamicin overdose.
- **Glycyrrhizin**

    Aldosterone-like substance in licorice, ingestion of large doses can cause fluid retention and sustained hypertension.

Cardioglycoside Toxicosis Including Red Squill and Scirriloside

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Digitalis Purpurea and Other Species of *Digitalis* - Foxglove

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Cardioglycoside Toxicosis Including Red Squill and Scirriloside
Most species	Hours	Days; often lethal	

Description

- Plant - An erect biennial herb, which can attain a height of 4 feet.
- Leaves - The leaf shape varies widely, depending on the particular strain and species of *Digitalis*. Leaves may be large and broad, up to 12 - 15 inches long, or small, narrow leaves, 3 - 4 inches in length.
- Flowers - Are born during the second year in large numbers (in a pendant raceme) on the tall stalk of the plant: tubular-bell-shaped with spots frequently found on the inside bottom surface of the tube. The flowers vary in color depending on the variety (yellow, white, lavender, violet or purple); with most wild plants bearing purple flowers.
- Seeds - Many seeds are present in the small dry capsules (the fruit of the plant).

Habitat

- A common garden flowering plant originally introduced from Europe.
- Now naturalized and locally common in open rich lands, logged-off areas and roadsides from British Columbia to northern California as well as numerous other localities.

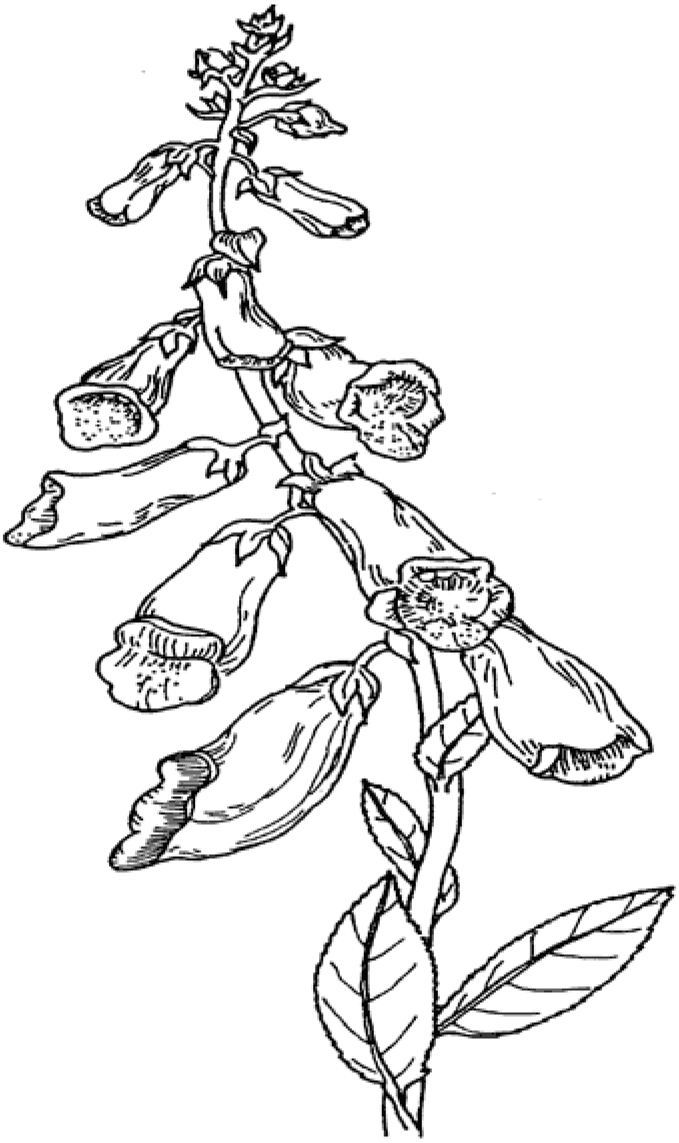
Toxic Principles

> Contains about a dozen chemically and physiologically related cardiac or steroid glycosides. These include digitoxin, digoxin, gitoxin and others.

Toxicity

- Drying does not reduce the toxicity of the plant.
- Poisoning has resulted in children from drinking the water in a vase containing foxglove plants.
- Eating the flowers, seeds or leaves may also cause toxicosis.

Signs, lesions, and treatment are the same as for **toxicoses induced from other sources of cardioglycosides.**



Foxglove (*Digitalis purpurea*)

Nerium - Oleander

Nerium oleander - Common pink oleander
N. odorum - Rose laurel, adelfa
N. indicum - Rosenlorbeer

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Cardioglycoside Toxicosis Including Red Squill and Scirriloside
Most species	Hours	Days; often lethal	

Family - Apocynaceae (dogbane family)

Description

- Plant - Evergreen shrub about 5 - 25 feet tall, looks like a small tree if all but one stem is cut; gummy, sticky sap.
- Stem - Bark smooth, green until several years old.

- Leaves - Simple, evergreen, leathery, narrow, entire, smooth edges, oblong lanceolate, sharply pointed, 4 - 12 inches long, whorled or sometimes opposite.
- Two primary parallel veins run perpendicular to the midrib.
- Flowers - Spring or early summer, showy, white, pink, yellowish, rose, deep red, large cluster.
- Fruit - Pods, several inches long, narrow, contain many seeds; seeds have a tuft of brown hairs; pods often not produced in USA.

Habitat

Native to Asia. Now an ornamental shrub in Southern and Southwestern USA. Common in Florida and widely planted in California. Sometimes used as a houseplant in the Northern USA.

Toxic Principle

- Highly toxic cardiac glycoside similar to digitoxin. The cardiac glycosides: nerioside, oleandroside, oleandrin, digitoxigenin, neriin and folinerin; oleandromycin (antibiotic), and rosagenin (strychnine-like).
- *N. indicum* contains odoroside (a steroidal glycoside).

Mechanisms of Action

- Specific action is inhibition of Na/K ATP-ase enzyme system; causing increased intracellular sodium and decreased potassium concentrations.
- Bradycardia and/or tachycardia.
- Severe hyperkalemia may occur. Serum potassium concentrations may increase 2-fold.
- Marginal hypocalcemia and hypoglycemia may occur.
- Oleander has pharmacodynamic effects on the autonomic and central nervous systems, on the myocardium and on the gastrointestinal tract. The predominant effects are in response to different forms of conduction alterations in the heart.

Susceptible Species

All.

Toxicity

- Stems, flowers, leaves are all toxic.
- Toxicity is not lost on drying.
- Garden cuttings thrown into dry lots are a major cause of poisoning.
- Since 400 B.C. oleander has been known to poison man via eating meat cooked over oleander branches, eating porridge stirred with oleander stems and eating honey manufactured from the nectar of oleander blooms.
- One leaf can kill an adult human.
- The glycosides are distributed throughout the plant, but growing tops may be most toxic; dried leaves and bark are also poisonous.
- Males may be more sensitive to toxic effects.
- Contact may produce dermatitis in sensitive individuals.
- Oleandrin has digoxin-like action and is only slowly eliminated from the body (1 - 2 weeks).
- Extracts from the common oleander have been used as potent rat killers, insecticides and fish poisons, and are extremely toxic to all mammals.
- Oleandrin is water soluble, so leaves falling in a pond can poison the water, but the water is usually made unpalatable, so animals may avoid it.
- Plant is bitter and usually avoided.
- Using oleander twigs as skewers for roasting hot dogs may cause toxicosis.
- Monkey.
  - The cumulative toxic dose was 30 - 90 mg/kg orally in divided doses of 7.5 and 30 mg/kg at intervals of 48 hours.
  - Survival times ranged from 33 - 341 hours. The toxic effect was negligible when a dose of 3 mg/kg was given even though a total cumulative dose of 60 mg/kg was administered.
- Mice, Rats, Chickens.
  - Relatively insensitive to the cardiac effects of Oleander; neurotoxic at high doses.

- Dog.
  - The cumulative toxic dose orally was 150 - 225 mg/kg in 3 divided doses of 50 - 75 mg/kg at intervals of 24 hours. Survival time ranged from 76- 90 hours.
  - When 2 dogs were anesthetized and administered oleander tincture at 20 and 25 mg/kg, the animals developed A-V conduction defects, bradycardia, and ventricular ectopic beats. Four dogs injected with 30 mg/kg of oleander extract died within 6 hours of dosing.
- Cat.
  - The cumulative toxic dose of dried oleander leaves was 220 and 450 mg/kg BW orally in divided doses of 37.5 and 75 mg/kg at intervals of 24 hours. Survival times included 114, 240 and 36 hours.
- Goats.
  - The cumulative toxic dose was 200 mg/kg orally in divided doses of 100 mg/kg at intervals of 24 hours. The survival time was 33 - 35 hours.
- Sheep.
  - Ingestion of just 2 or 3 leaves is lethal.
  - One to 5 grams is toxic to sheep (green or dry).
- Cattle.
  - Lethal dose is 1 - 20 grams (green) or 15 - 25 grams (dry) leaves.

Signs

- General.
  - Onset is usually several hours after ingestion.
  - Signs may persist for 24 hours after plant material is evacuated from the gastrointestinal tract.
  - Signs are mainly referable to the heart and gastrointestinal tract.
  - Local irritation of the mucous membranes of the mouth and stomach.
  - Abdominal pain, nausea, vomiting, sweating in some species.
  - Anorexia.
  - Digitalis-like effects on the heart (pulse rapid and weak or slow and strong, depending on the stage of the disease).
  - Constriction of the blood vessels, cold extremities.
  - Pupillary dilation, blurred vision, fever.
  - Dizziness, drowsiness, ataxia.
  - Colic, bloody diarrhea (may be severe).
  - Cardiac arrhythmias, unconsciousness, hypotension, hypothermia, bradycardia.
  - Respiratory paralysis, dyspnea, shallow breathing.
  - Tremors followed by progressive paralysis, coma and death (fibrillation in terminal stages).
- Goat.
  - Bleating and suppressed ruminations in addition to general signs.
- Man.
  - Excessive salivation, nausea, vomiting, mydriasis, incoordination, depression, prostration, convulsions, dyspnea, cyanosis; contact dermatitis.

Lesions

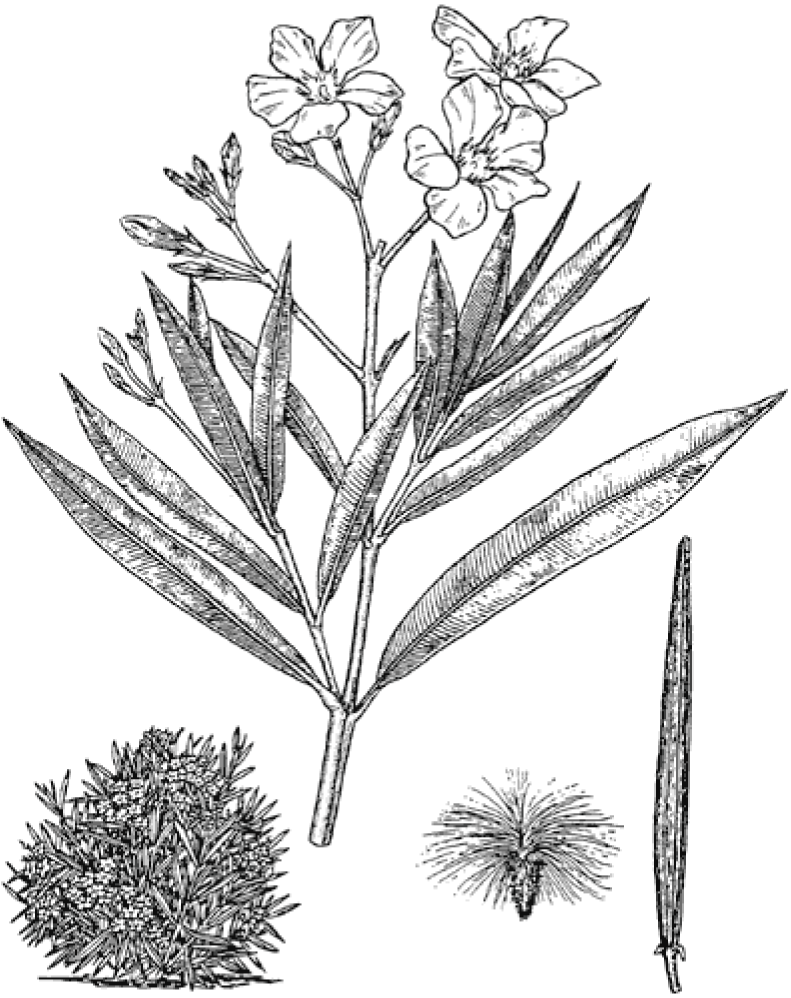
- General.
  - Severe catarrhal or hemorrhagic gastroenteritis.
  - Agonal hemorrhages are commonly encountered on the heart and serous and mucous membranes.
  - Clear or blood-stained fluid may be present in the serous cavities.
- Monkeys.
  - Pale mottling of the myocardium; subepicardial and subendocardial hemorrhage.
  - Hemorrhagic gastroenteritis and colitis.
  - Contraction of the myocardium, gall bladder and uterus.
  - Endometrial hemorrhage.
  - Multiple focal hemorrhages of the skeletal muscles.
  - Subcapsular ecchymoses of the ovaries and adrenals.
  - Congestion of the liver, lymph nodes, thyroid and adrenals.
  - Pancreatic weight reduced, adrenal weights increased.
- Goats.
  - Similar to monkeys, plus aspiration of rumen contents and foreign body pneumonia.

Diagnosis

Identification of oleander, evidence of consumption, and appropriate clinical signs and lesions.

Treatment

- Treat as for other cardioglycoside toxicoses.
- Dipotassium edetate has been used in the treatment of Oleander toxicosis and acts by antagonizing the cardiotoxicity via increasing membrane permeability through reduction of the calcium ion concentration and, consequently enhanced re-entry of potassium ions into the cardiac myofibers.



Oleander (*Nerium oleander*) - The narrow leathery leaves, the colorful flowers, and the hairy seed and slender seed pod (lower right) are characteristic of this deadly plant.

Convallaria - Lily of the Valley

Convallaria majalis - Lily of the Valley
C. montana

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Cardioglycoside Toxicosis Including Red Squill and Scirriloside
Most species	Hours	Days; potentially lethal	

Family - Liliaceae (Lily family)

Description

- *C. majalis.*
    - Plant - Perennial herb, usually forming a dense mat that is persistent and excludes other plants.
    - Leaves - Basal, broad, 2 oblong, to oval, smooth.
    - Flower - Slender stalk bears a 1-sided row of waxy, bell-shaped, tiny white or pale pink, nodding, fragrant flowers.
    - Fruit - Fleshy, red, orange, 1/2 inch in diameter berry; seldom forms.
    - Rootstock - Horizontal.

Habitat

- *C. majalis.*
    - Escaped from cultivation in flower gardens throughout the USA and Canada.
- *C. montana.*
    - Virginia and Georgia, native to the high mountain areas of the southern states.

Toxic Principle

Cardiac glycosides - Convallarin, convallamarin, and convallatoxin.

Susceptible Species

Livestock (all), pets, humans.

Toxicity

- Leaves, flowers, roots are toxic; berries may also be toxic.
- Cardiac glycosides in all parts of the plant; both green and dried.
- A child died after drinking the water from a vase containing Lily of the Valley.
- Dermatitis can occur upon contact with the leaves.
- Has a purgative effect.

Signs

- Cardiac signs may be delayed for days and may persist for 3 weeks.
- The heart becomes hyperirritable and premature ventricular contractions and ventricular tachycardia may occur.
- Leaves may cause dermatitis.
- Vomition, diarrhea, nausea, anorexia, cramps.
- Large dose.
    - Mental confusion, extreme weakness, depression.
    - Collapse of circulation and death.

Lesions

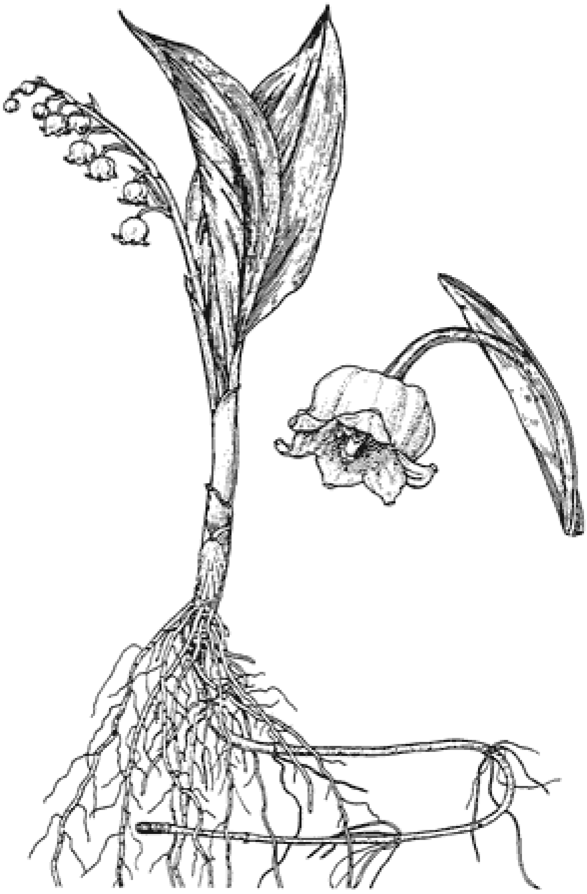
Gastroenteritis.

Diagnosis

Identification of Lily of the Valley, evidence of consumption, and appropriate clinical signs and lesions.

Treatment

Treat as for digitalis overdose, recognizing the need for sufficiently sustained therapy.



Lily of the Valley. - The delicate white fragrant flowers (enlarged, right), the long lance-shaped leaves, and the horizontal rootstocks are characteristic of this hardy ornamental.

Apocynum - Dogbanes

Apocynum androsaemifolium - Spreading dogbane
A. cannabinum - Hemp dogbane, Indian hemp
A. sibiricum - Prairie dogbane

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Cardioglycoside Toxicosis Including Red Squill and Scirriloside
Most species	Hours	Days; potentially lethal	

Family - Lily of the Valley, Apocynacea (dogbane family)

Description

- *A. androsaemifolium.*
    - Plant - Perennial, erect, 1 - 1 3/4 feet tall, contains milky juice.
    - Stem - Somewhat woody, smooth.
    - Leaves - Opposite, paired, smooth margined, ovate to oblong, mucronate tipped, slender petioled, dull dark green and smooth above; pale and somewhat pubescent below, loosely spreading or drooping.
    - Flowers - Fragrant, mostly nodding; cymes flowers simultaneously, terminal one is usually largest; corolla pink.
    - Fruit - Pods long, narrow, pencil-like, cottony mass within; seeds long, narrow, each with a tuft of long white hairs.
    - Rootstock - Spreading.

- *A. cannabinum.*
    - Plant - Erect perennial herb which grows to 5 feet tall. Contains milky juice.
    - Leaves - Opposite, simple untoothed.
    - Flowers - Small pinkish, appear in early summer.
    - Fruit - Slender, 2 inches long, hanging follicle or shoot which hangs in pairs and contain long, narrow seeds; seeds are covered with long silky hairs.

Habitat

Widely distributed in the USA and Canada. Open places, coarse soil, along streams, roadsides, pastures and infrequently tilled fields.

Toxic Principle

Cardiac glycosides.

Susceptible Species

Horses, cattle and sheep.

Toxicity

- Fifteen to 30 grams of green leaves has been reported as causing death of a horse or a cow.
- Reportedly very distasteful and animals usually avoid; poisoning is thus infrequent. Consumed primarily when other forage is in short supply.
- Green and dried dogbane is toxic.
- The root of *Apocynum cannabinum* has been employed therapeutically to "retard the heart in systole" and was therefore used for "dropsy" and "heart trouble".

Signs

- Increased temperature and heart rate (or slow heart rate).
- Coldness of extremities.
- Dilation of pupils.
- Discoloration of mouth and nostrils, sore mouth.
- Sweating, gastric upset.
- Death.

Lesions

Nonspecific.

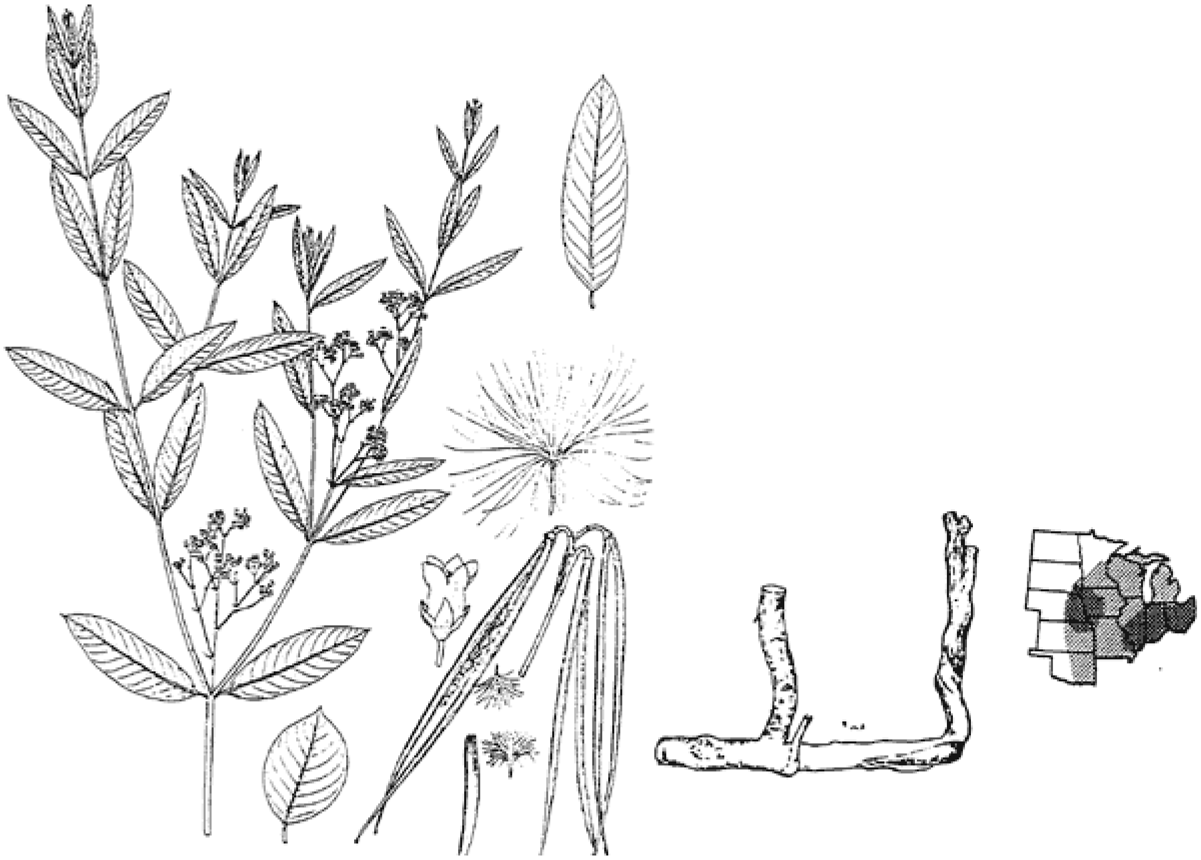
Diagnosis

Identification of *Apocynum*, evidence of consumption and appropriate clinical signs.

Treatment

Treat as for digitalis overdose, recognizing the need for sufficiently sustained therapy.

Note - Although still regarded as toxic, some of the literature is based upon confusion of *Apocynum* with *Nerium*, both members of the Apocynaceae family.



Dogbane - Note the paired, entire, variable-shaped leaves, the clusters of small flowers (enlarged, right), and the slender pods and tufted seeds (far right) of this milky-juiced herb.

Bufo Toxicosis - Toad Poisoning

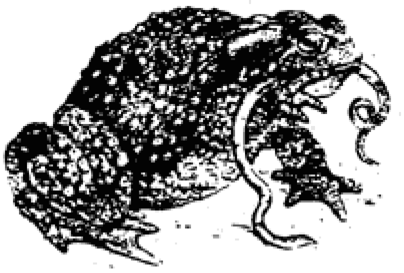
Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Cardioglycoside Toxicosis Including Red Squill and Scirriloside
Dog, cats	Minutes to hours	Days; often lethal	

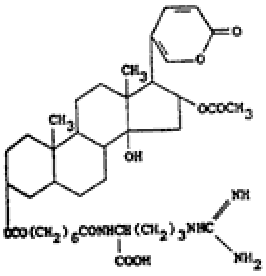
Source

- The giant tropical toad, *Bufo marinus*, was introduced to the southern states and Hawaii approximately 40 years ago for insect control. The toads produce toxin in the parotid glands which are situated behind the tympanum and extend backward over the shoulders. There are numerous pin hole openings on the surface skin of these glands from which toxin can be manually expressed. The toads, therefore, are a threat to unsuspecting people who may be exposed to the toxin through an open wound, but more commonly, the threat is to animals mouthing the toads.
- *Bufo alvarius* also produces similar toxic secretions.

Toxic Principle

- The parotid gland secretions of *Bufo* toads contain bufagins, bufotoxins, bufotenins, and other compounds. Bufotoxins are conjugated bufagins. Bufagin's and bufotoxin's action is described as digitalis-like, often resulting in ventricular fibrillation. Bufotenins have oxytocic action and frequently a marked pressor action.
- Other compounds found in *Bufo* toxin are epinephrine, cholesterol, ergosterol, and 5-hydroxytryptamine (5-HT) (also called serotonin or "serum vasoconstrictor").





Bufo marinus Bufotoxin

Species Affected

Canine, feline rarely.

Toxicity

The *Bufo marinus* in Florida seems to produce a more potent toxin than that produced by the Hawaiian or Texan *Bufo marinus*. Mortality in Hawaii of exposed and untreated dogs is approximately 5% as compared with nearly 100% in Florida.

Signs

- Signs vary according to the animal's age, concurrent disease, amount of toxin absorbed, and length of time since exposure.
- There are three primary aspects to *Bufo* toxicosis: **a**) the cardiac glycoside-like effects of the bufagins; **b**) the pressor effects of the catecholamines, and **c**) the hallucinogenic effects of the indolealkylamines.
- Salivation, head shaking.
- Ataxia, polypnea, emesis, diarrhea.
- Increased respiratory rate and depth.
- Apparent blindness.
- Convulsions.
- In early intoxication, monitoring reveals a gradual deterioration of the ECG with progressive negative ventricular deflection. This eventually results in ventricular fibrillation and death if untreated.

Clinical Pathology

- Moderate increase in packed cell volume, hemoglobin content, and icterus index.
- Increase in blood glucose, blood urea nitrogen (BUN), potassium, and calcium.
- Sedimentation rate increases.
- Serum sodium and chloride concentrations decrease slightly, but serum inorganic phosphorus content is markedly reduced.
- Total protein usually decreases.
- Total white blood cell count decreases, principally because of neutropenia.
- Initial spike of SGOT which returns to normal.

Treatment

- First, when possible it is highly important to rinse mouth thoroughly. Often practitioners recommend using a garden hose to rapidly rinse *Bufo* secretions from the oral mucous membranes. Follow with activated charcoal and a saline or sorbitol cathartic. Activated charcoal may be repeated after 2 hours.
- In a patient **without** a history of asthma or cardiac disease:
  - Administer pentobarbital anesthesia.
  - Insert endotracheal tube.
  - Wash mouth out vigorously with running water.
  - Administer propranolol - 2 mg/kg body weight, IV; normal heart rate should return within 15 seconds.
  - Monitor ECG, repeat propranolol after 20 minutes if necessary.
  - **Note** - These doses of propranolol are for *Bufo* intoxication **only**.

    - Administer fluids if considered appropriate.
- If asthma or cardiac disease signs or history exist:
    - Monitor ECG and administer propranolol IV slowly at 0.5 mg/kg BW until cardiac rate returns to normal.
    - Administer fluids if appropriate.
    - Animals should be monitored for at least 24 hours after exposure.
- For life-threatening hyperkalemia, administration of glucose, insulin, and bicarbonate (slow IV in the fluids) is recommended. ECG monitoring during administration is warranted.
- Atropine may be of value for asystole and/or bradycardia.
- Phenytoin or lidocaine may be warranted for unresponsive clinically significant arrhythmias in small animals.
- A recent report described the use of Digibind ® (digoxin antibody fragments) for life threatening toxicoses in young men caused by chan su, which contains various bufo toxins.

Note

Anesthetics may further compromise an already diseased myocardium and should be used with discretion. Also, beta-adrenergic blocking drugs such as propranolol may block the endogenous catecholamines that asthmatics depend on for bronchodilation, and that animals with heart failure depend on to drive the heart. They should, therefore, be used with caution in older, asthmatics or cardiac diseased dogs.

Additional Toxicants

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Cardioglycoside Toxicosis Including Red Squill and Scirriloside
Red squill (rodenticide)	Dogs, cats	Minutes to days	Days; often lethal; not widely available	
Scilliroside (rodenticide)	Dogs, cats	Minutes to hours	Days; often lethal; not widely available	
Some milkweeds (*Asclepias*)	(See Toxicants Associated with CNS timulation or Seizures)			

Andromedotoxin (Grayanotoxin) - Containing Plants (Heath, Ericaceae Plant Family)

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Rhododendron

Rhododendron albiflorum - Rhododendron
R. occidentalis - Western azalea, white laurel
R. californicum - Rhododendron, California rose bay
R. catawbiense - Rose bay
R. maximum - Great laurel

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Andromedotoxin (Grayanotoxin) - Containing Plants (Heath, Ericaceae Plant Family)
Esp. goats, most species	Hours	Several hours to days; often lethal	

Family - Ericacea (Heath family)

Description

- *R. albiflorum.*
    - Plant - Erect, deciduous shrub, 3 - 6 feet tall.
    - Stem - Woody.
    - Leaves - Thin, elliptical, 1 1/2 - 3 inches long.
    - Flowers - Axillary, creamy white, in groups of 1 - 3
    - Fruit - Capsule.
- *R. occidentalis.*
    - Plant - Deciduous, shrub 3 - 9 feet tall.
    - Stem - Slender.
    - Leaves - Thin, alternate, elliptical, entire, 2 - 3 1/2 inches long.
    - Flowers - Terminal, white with yellow or pink markings.
    - Fruit - Capsule, oblong, 3/4 - 1 inch long.
- *R. californicum.*
    - Plant - Evergreen shrub or small tree, 3 - 15 feet tall.
    - Stem - Coarse, branched.
    - Leaves - Alternate, elliptical, entire, 4 - 11 inches long.
    - Flowers - Terminal, dense, show, rose-white, 1 1/2 inches across.
    - Fruit - Capsule, subcylindrical, 1/2 inch long.
- *R. maximum.*
    - Plant - Large, evergreen, shrub or open tree, 35 feet tall.
    - Leaves - Alternate, oblong, 4 - 10 inches long, acute at both ends.
    - Flowers - Dense, showy, rose to pink or white or mixed.

Habitat

- *R. albiflorum*: Pacific Northwest.
- *R. occidentalis*: California.
- *R. californicum*: California to Washington and British Columbia.
- *R. catawbiense*: Allegheny Mountains, Virginia to Georgia.
- *R. maximum*: New York southward to Georgia, Allegheny Mountains.
- General.
    - Found mostly in moist/wet soils.

Toxic Principle

The glycoside, andromedotoxin. Now commonly referred to as grayanotoxin.

Mechanism of Action

Grayanotoxin stabilizes voltage-sensitive sodium channels in the open position. Because of the influx of sodium, effects on the heart may resemble those of digitalis (which inhibits Na-K ATPase).

Susceptible Species

Cattle, sheep, goats, rarely horses, people, etc.

Toxicity

- Leaves are tough, and sometimes regarded as bitter and unpalatable.
- All parts of the plant, but especially the foliage, contain the poison.
- Two or 3 leaves may produce severe toxicosis.
- Sucking flowers free of nectar may produce serious illness.
- Most toxicoses occur in the winter and early spring, when other forage is unavailable. Rhododendrons are more likely to retain green leaves year round than are most other plants.
- Approximately 0.2% of the BW is a toxic dose.

Signs

- Clinical signs generally appear within 6 hours of ingestion.
- Acute digestive upset, salivation, nasal discharge, epiphora.
- Anorexia, depression, nausea, projectile vomiting, frequent defecation, repeated attempts to swallow.
- Weakness, incoordination, paralysis of the limbs, stupor, depression of the heart and central nervous system.
- Aspiration of vomitus is common in ruminants and results in dyspnea and often death.
- Pupillary reflexes may be absent.
- Coma precedes death.
- Animals may remain sick for more than 2 days and gradually recover.

Lesions

- Gastrointestinal irritation with some hemorrhage.
- Renal tubular damage.
- Mild liver degeneration is sometimes present.
- Aspiration pneumonia.

Diagnosis

Identification of *Rhododendron*, evidence of consumption and appropriate clinical signs and lesions.

Treatment

- Prevent absorption.
    - Emesis for appropriate species if not contraindicated.
    - Activated charcoal and a saline or sorbitol cathartic. Repeat activated charcoal as a dilute slurry at 2, 5, 8, and 12 hours.
- Atropine as needed for bradycardia.
- Intravenous fluid therapy.
- Antiarrhythmics may be warranted in seriously affected animals that do not respond with the therapy given above.

Rhododendron and Azalea
Colorful flowers and attractive leaves characterize these beautiful ornamental shrubs.

Kalmia - Laurels

Kalmia angustifolia - Lambkill, sheepkill, calfkill, dwarf laurel, wicky
K. latifolia - Mountain laurel, calico bush, ivy bush
K. polifolia* var. *microphylla - Pale laurel, bog laurel

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Andromedotoxin (Grayanotoxin) - Containing Plants (Heath, Ericaceae Plant Family)
Esp. goats, most species	Hours	Several hours to days; often lethal	

Family - Ericaceae or heath family

Description

- *K. angustifolia.*
    - Plant - Open woody shrub, rarely 3.5 feet tall.
    - Stem - Branches are strongly ascending.
    - Leaves - Opposite or in threes, pale green and glabrate underneath, bright green above, narrowly oblong, obtuse, petioled, leathery, 2 - 5 cm long, persist through the winter.
    - Flowers - Many, showy, crimson or rose, rarely 1 cm across; calyx is glandular; inflorescence is corymbose and produced laterally on the stem, perfect, regular, slightly glandular.

    - Fruit - Pod depressed, nearly smooth, 5 cavitied, many seeded capsule.
- *K. latifolia.*
    - Plant - Evergreen shrub-tree, dense, woody, round-topped, 3 - 10 feet tall.
    - Leaves - Alternate, both sides are bright green, ovate-lanceolate or oblong, acute at each end, petioled, coriaceous, evergreen, entire, 2 - 5 inches long.
    - Flowers - Many, showy, clammy-pubescent, pink or white, inflorescence corymbose, produced at stem tips, rose-white with purple markings, 0.6 - 1 inch across.
    - Fruit - Pod depressed, glandular, many seeded.

Habitat

- *K. angustifolia.*
    - Northeastern USA (Appalachian Mountains), rocky hillside woodlands, acid soils, nonfertile soils, abandoned pastures, meadows.
- *K. latifolia.*
    - Eastern USA. Rocky wooded areas, clearings, rocky slopes, gardens.
- *K. polifolia.*
    - California to Alaska. Wet meadows and bogs, Rocky Mountains.

Toxic Principle

Andromedotoxin (grayanotoxin).

Mechanism of Action

See *Rhodendron* and *Pieris* sections.

Susceptible Species

Sheep, cattle, horses, goats, people, etc.

Toxicity

- General.
    - Leaves are tough and leathery, animals often avoid; most cases of poisoning occur in winter or early spring when *Kalmia* spp. are the only conspicuously green plants available.
- *K. latifolia.*
    - Minimum toxic doses: Cattle - 0.4% of BW, goats 0.4%, sheep, 0.35% (similar doses in various species of ruminants).
    - The poisonous principle is present in all parts, foliage is especially hazardous.
    - Honey made from these plants may be poisonous.
    - Children have been poisoned by chewing leaves or sucking juice from blossoms or by making "tea".
    - Deer may tolerate ingestion of *K. latifolia*.
    - Grouse have been known to feed on *K. latifolia* fruit in winter and were not apparently affected.
    - It has been suggested that poisoning may result from the eating of flesh from animals that had eaten *Kalmia*.

Signs

- General.
    - Signs appear within 3 - 14 hours of ingestion.
    - Weakness, nausea, intense abdominal pain, repeated swallowing.
    - Salivation, epiphora, runny nose, vomiting.
    - Dyspnea may occur; heart rate slows.
    - Depression, prostration.
    - Convulsions,paralysis of limbs, coma.
    - Possible death within 12 - 14 hours.
    - May live several days and die from foreign body pneumonia or recover.

- Cattle.
    - Soft, liquid feces, diarrhea.
    - Partial loss of control over hind limbs.
    - Muscular incoordination.
    - Pulse becomes weak, expiration forced, respiration shallow.
- Goat.
    - Regurgitation, nausea.
    - Weak pulse, irregular respiration, groaning on expiration.
- Sheep.
    - Forced, short, shallow respiration.
    - Grating of the teeth.
    - Depression, salivation, regurgitation.
    - Inability to stand, unsteady gait.
    - Head drooped and extended. Animals may present in lateral recumbency and exhibit paddling.
    - Watery, foul-smelling feces.
- Cat.
    - Epiphora, salivation, nasal discharge.
    - Slight fever (102.5).
    - Involuntary paddling of the limbs.
    - Intermittent running "fits".
    - Arching of the back; paralysis of the limbs.
    - Death.
- Also see *Kalmia* and *Pieris* sections.

Lesions

- Fragments of glossy, leathery leaves in the gastrointestinal tract.
- Congestion of the gastric (abomasal) mucosa, duodenum, ileum, kidneys.
- Pneumonia if aspiration has occurred.

Diagnosis

Identification of *Kalmia*, evidence of consumption, and appropriate clinical signs and lesions.

Treatment

See *Rhododendron* section.

Pieris - Japanese Pieris

Pieris japonica - Japanese pieris
P. floribunda

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Andromedotoxin (Grayanotoxin) - Containing Plants (Heath, Ericaceae Plant Family)
Most species	Hours	Several hours to days, often lethal	

Family - Ericaceae (Heath family)

Description

- Plant - Woody shrub or small tree; 30 feet tall when mature.
- Leaves - Alternate, obovate-lanceolate, 1 1/2 - 3 inches long, margins finely toothed.
- Flowers - Small, 1/4 inch across, white, terminal on stem; inflorescence paniculate; 10 stamens.

- Fruit - Capsule.

Habitat

- *P. japonica.*
    - Japan, Oregon, Washington, Montana, British Columbia, New York. Ornamental, wet places in higher elevations, mountains.
- *P. floribunda.*
    - Virginia to Georgia.

Toxic Principle

Andromedotoxin (grayanotoxin).

Mechanism of Action

See *Rhododendron* section.

Signs, Lesions, Diagnosis, Treatment

- See *Rhododendron* and *Kalmia* sections.
- Also donkeys exhibited tachycardia, dyspnea, green froth around the mouth, minimal gut activity, paralysis, and inability to open their jaws. Paralysis subsided after four days.

Cardioglycoside-Like Plants

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Aconitum - Monkshood

Aconitum columbianum - Western monkshood
A. napellus - Aconite, garden monkshood
A. lutescens - Yellow monkshood
A. uncinatum - Wild monkshood
A. lycoctonum
A. reclinatum
A. vaccarum

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Cardioglycoside-Like Plants
Most species	Hours	Days; often lethal	

Family - Ranunculacea or crowfoot family

Description

- *A. columbianum.*
    - A perennial herb, 3 - 6.5 feet tall with alternate, roundish, divided, palmately arranged segments, with pointed tips. The leaves are 2 - 3 inches across, lobed, hairy and sticky. Flowers are perfect, showy, blue or white, with a prominent hood. Fruit is a several seeded pod.
- *A. napellus.*
- A perennial herb with an ascending or trailing stem and alternate, palmately lobed (3 - 9 divisions) leaves. Flowers are of characteristic helmet shape, in terminal clusters, blue, white, pink, or deep blue-purple. Fruit is comprised of 3 - 5 separate follicles, with many tiny seeds.

- *A. reclinatum.*

- A 1 - 5 feet tall perennial herb, with roundish 2 - 3 inch wide leaves, which have palmately arranged segments with pointed tips. Flowers are white, bilaterally symmetrical with hood or helmet shape. Fruit (3 - 5) which ripen into a cluster of follicles containing many seeds (tiny).

Habitat

- *A. columbianum.*
    - Northern Rocky Mountain states, Pacific coast states; New Mexico to Canada. Wet meadows, along streams, high altitudes.
- *A. napellus.*
    - Northeastern states and Canada. Garden plant.
- *A. lutescens.*
    - Idaho to New Mexico.
- *A. uncinatum.*
    - Pennsylvania to Georgia. Shaded soil along streams.
- *A. reclinatum.*
    - Georgia to New York and west to Ohio. Rich, moist soils in woods, slopes along waterways.

Toxic Principle

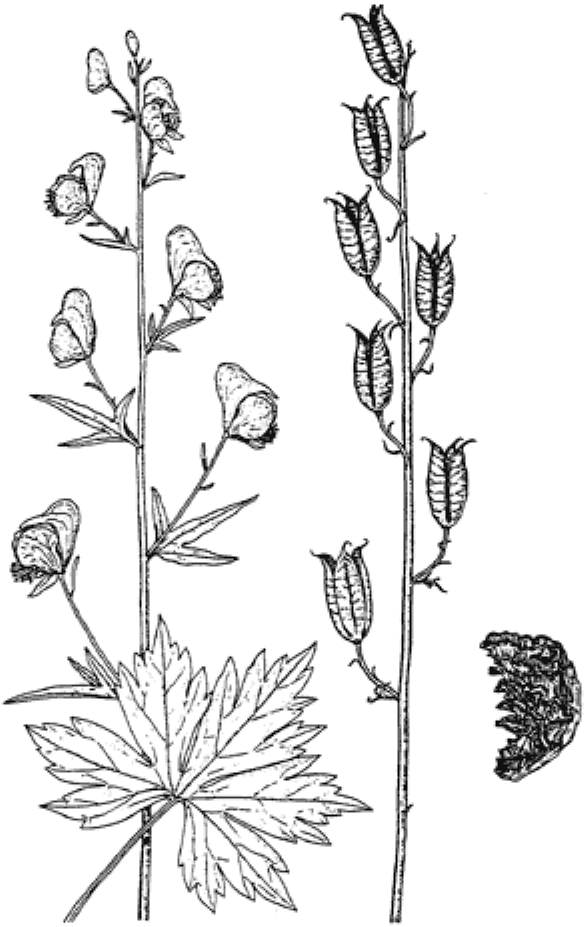
Alkaloids - aconitine, aconine, perhaps several others.

Toxicity

- The alkaloids occur in all parts of the plant, but especially in the roots and seeds.
- Toxicity varies with climate and stage of growth.
- Leaves are most poisonous just before flowering.
- The extremely toxic root can be mistaken for a wild horseradish.
- Ingestion of a small amount of juice may be fatal in a few hours.
- Note 0.075% of the body weight ingested may be fatal to a horse.

Signs

- General signs include oral irritation, dizziness, nausea, severe vomiting, diarrhea, slow and weak heartbeat, muscular weakness, restlessness, salivation, and dyspnea.
- Bloating, prostration, belching, frothy salivation, frequent swallowing, anxiety, convulsions and death.
- With *A. columbianum*, death has occurred at 6 hours after ingestion.
- With *A. reclinatum* and *A. uncinatum* death may occur from a few hours to a few days after ingestion.
- Cardiovascular disturbances including hypotension and myocardial depression have been described. The arrhythmias accompanying these effects, which may be difficult to manage pharmacologically, consist primarily of supraventricular tachycardia and conduction disturbances. It has been suggested that these be managed as cardioglycoside overdose



Western Monkshood
The hooded, dark blue flowers, the palmately lobed leaves, the beaked capsule, and rough seed (enlarged, lower right) are characteristic of this dangerous plant.

Additional Toxicants

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Cardioglycoside-Like Plants
Mistletoe (*Phoradendron*)	(See Plants that Affect Gastrointestinal Tract)			

Other Plants that Affect the Heart

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Taxus - Yew

Taxus canadensis - American Yew, Ground Hemlock
T. cuspidata - Japanese Yew
T. baccata - English Yew
T. brevifolia - Western Yew

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Other Plants that Affect the Heart
Most species	Hours	Days; often lethal	

Family - Taxaceae (Yew Family)

Description

- *Taxus* spp.
  - Plant - Evergreen gymnospermous trees of small erect or decumbent shrubs.
  - Stem - Bark, reddish-brown, thin, flaking in thin scales.
  - Leaves - Alternate, needle-like, often shaped like a narrow sickle, spirally arranged, linear, stiff, 1.25 - 2.54 cm long (0.5 - 1 - 1/2 inches), midrib prominent, dark green to yellow-green, spread in 2 ranks; winter buds have overlapping scales; prominent midvein; 2 yellowish green veins on under surface, no resin ducts. Abruptly pointed or gradually long-pointed at apex. *Leaves of Japanese Yew are wider than Canada Yew.
  - Flowers - Axillary, inconspicuous, unisexual, small.
  - Fruit - Seeds, stony, solitary, borne in cup-shaped, fleshy, bright scarlet, red, thick, ovoid, aril, showy, appear as a red or yellow berry, 1.25 - 1.85 cm (0.5 - 0.75 inches).

Habitat

- *T. canadensis.*

  Kentucky to northeastern states and Canada, native to N. America, Newfoundland to Quebec and Manitoba, South to Virginia, Kentucky, Ohio, Indiana, Illinois and Iowa. Coniferous wooded slopes, ravines, along marshes, bogs, stony deciduous forests and cliffs.

- *T. cuspidata.*
  - Northern states; native of Japan, Manchuria and Korea. Widely used as an ornamental.
- *T. baccata.*
  - Southern states and as far north as New York. Ornamental.
- *T. brevifolia.*
  - Pacific states to Montana, native to North America, coast from Alaska and British Columbia, South to California and eastward to Montana. Forests, wooded slopes, singly or in small groups, deep soils along streams and moist flats near the coast.

Toxic Principle and Mechanisms of Action

- Perhaps an alkaloid, taxine.
- Separated into 2 fractions, taxine A and B.
- Taxine B is present in the greatest amount.
- As many as 10 alkaloids have been isolated.
- The alkaloid does not act as a cardiac glycoside, but depresses conduction of depolarization through the heart.

- No alkaloids found in *T. brevifolia*.
- Also, a volatile oil that acts as a slow acting gastrointestinal irritant.

Susceptible Species

- All livestock, humans, dogs and wild animals.
- Monogastrics are more sensitive.

Toxicity

- General.
    - Wood, bark, leaves, and seeds are toxic in the dry or green state.
    - The concentration of taxine is greater in old leaves, than young leaves.
    - Taxine concentration in leaves is maximal in the winter.
    - The red pulp of berries seems to be harmless.
    - The seed is quite toxic but must be chewed.
    - Large doses are readily consumed by livestock.
    - Clippings from bushes cause most instances of poisoning.
    - Most dangerous of all poisonous trees or shrubs in Great Britain.
    - Toxic all seasons of the year.
    - Common cause of lethal poisonings in large animals in Midwest USA.
- *T. baccata*
    - Green foliage is toxic to monogastric animals at 0.1% of an animal's body weight.
    - Green foliage is toxic to ruminants at 0.5% of the animal's body weight.
    - LD_{50} in mice is 15 mg/kg.
    - LD_{50} in rabbits is 8 mg/kg.
- *T. cuspidata*
    - The toxicity of *T. cuspidata* may be greater than *T. baccata*.
    - About 0.1% of a 5 year old Shetland pony's weight of green *T. cuspidata* produced death within 1.25 hours after feeding. The foliage was finely ground and administered via a stomach tube.

Signs

- General
    - Up to 2 days may pass before clinical signs appear but generally occur rapidly.
    - Nervous signs including trembling, dyspnea, incoordination and collapse.
    - Acute cardiac failure, bradycardia.
    - Gastroenteritis, diarrhea.
    - Rapid death due to cardiac failure - heart stops.
    - Ingestion of small amounts may cause vomiting, nausea, diarrhea, abdominal cramps, trembling, difficulty breathing and dilated pupils.
- Human.
    - Weakness, trembling, diarrhea, and vomiting.
    - Slow heartbeat, difficulty breathing.
    - Hypotension and red spots on various parts of the body.
    - Convulsions and coma.
- Shetland Pony.
    - Paw ground as if hungry for nearby grass.
    - One hour after dosing, lower lip hung limp as if paretic.
    - Tail hung limp.
    - Pulse weak (not palpable over external maxillary artery).
    - Ataxic gait similar to "Equine Wobbler", especially of rear limbs.
    - Intermittent trembling of leg muscles.
    - Audible respiratory grunt.
    - Collapse to knees and lateral recumbency when led about.
    - Short convulsions.
    - Legs and body rigid, followed by 30 seconds of paddling with limbs.
    - Death followed appearance of first signs in less than 15 minutes.
- Cattle.
    - Usually no lesions, death attributed to lightning, etc.

    - Occasionally dependent edema, pulmonary edema, etc., acute in onset.
- Dogs.

    Tetanic epileptiform seizures reported, not experimentally reproduced.

Lesions

- Taxine depresses the conduction system of the heart, therefore there are no significant lesions, although plant material is consistently found in the digestive tract.
- Moderate irritation may be found in the upper GI tract with acute poisoning.
- Pulmonary congestion and edema, and splenic congestion occurred in 7 and 10 year old Brahman-type bulls.

Diagnosis

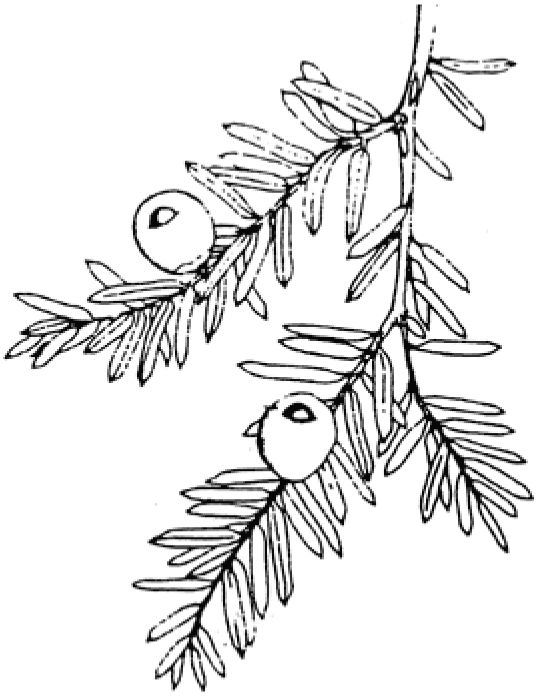
Identification of *Taxus* spp., in stomach or rumen contents (evidence of consumption) and appropriate clinical signs often including death.

Note

It may be necessary to examine a horse's stomach contents with a dissecting microscope because mastication may make identification otherwise impossible. Examine carefully in any species as foliage can easily be missed.

Treatment

- No specific treatment for taxine.
- Remove animal from source of plant insult.
- Establish respiration.
- Induce emesis unless contraindicated, gastric or rumen lavage.
- Endotracheal intubation preceding gastric lavage in small animals.
- Activated charcoal and saline cathartic.
- Atropine to counter the depressant effect of taxine (must be given early to have any benefit).
- Maintain body fluid and electrolyte balance.



Yew (*Taxus baccata*)

Cassia - Senna, Coffee Senna

Cassia fasciculata - Senna
C. lindheimeriana
C. occidentalis - Coffee senna
C. tora - Sickle pod
C. fistula

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Other Plants that Affect the Heart
Cattle, fowl and other species	One day to chronic	Days to permanent damage; often lethal	

Family - Leguminosae (pulse or bean family)

Note - Do not confuse with *Sesbania*.

Description

- *C. occidentalis.*
  - Plant - Annual.
  - Leaves - Leaflets, 4 - 6 pairs, ovate-lanceolate, acute, ovate, gland at base of petiole, drab green.
  - Flower - Bright, golden yellow.
  - Fruit - Pod, long, linear, 4 3/4 inches long, glabrous, green with transverse brown bars.
- *Cassia* spp.

- Plant - Annual/perennial herb.
- Leaves - Simple, abruptly pinnate, alternate; leaflets, 4 - 6.
- Flower - Mostly yellow, axillary or terminal, conspicuous, slightly irregular; sepals, 5; scarcely united at base; petals, 5; stamens, 5 - 10, unequal, often imperfect, spreading.
- Fruit - Pod, long, many seeded, often with cross partitions, may be 4-sided.

Habitat

- *C. fasciculata.*

  Texas, east of Mississippi river, sandy soil.

- *C. lindheimeriana.*

  Texas to southern Arizona and New Mexico.

- *C. occidentalis.*

  South East of United States, from Virginia and eastern Kansas to Florida and Texas; native to the tropics; eastern half of Texas.

- *C. tora.*

  Eastern United States; Pennsylvania to Kansas, South to Florida, Texas, and Mexico.

- *C. occidentalis, C. tora.*
  - Rich soil, river bottom pastures; weeds of hay and grain crops in Florida; waste places in east and south Texas.

Toxic Principles

- Substituted quinones occur in many species of *Cassia* and may be responsible for cathartic effects.

- *C. fasciculata* seeds have cathartic effects.
- *C. occidentalis*, *C. tora* causes skeletal and cardiac myodegenerative and sometimes hepatotoxic effects.
- Toxin exists in beans, leaves and stem and is water soluble. It may possibly be a peptide but its identity remains to be established.

Mechanism of Action

- Originally theorized as being due to uncoupling of oxidative phosphorylation in skeletal muscle mitochondria. However, this was disproven since mitochondrial damage was preceded by degeneration of myocardial fibers.
- Abnormal electrocardiographic patterns occur in terminal stages of illness including tachycardia, alteration in QRS complex, displacement of the ST segment and tenting of T-waves. The abnormal EKGs were mainly due to hyperkalemia, and alterations in the conduction of impulses in the heart was not pronounced.
- Thus these proposed mechanisms of action do not appear to be valid.
- The most recent theory indicates a high blockade of electron transport (rather than an uncoupling of oxidative phosphorylation).

Toxicity

- *Cassia occidentalis.*
    - All parts are toxic.
    - Duration of illness is inversely proportional to the daily dose rate, but not directly related to total dose.
    - Dried plant remains toxic.
- *Cassia occidentalis.*
    - One percent of body weight fed for 7 days generally produces clinical toxicosis.
    - Ground beans (*C. occidentalis*) given orally, at rates of 0.05 - 2% of body weight produced toxicosis in 26 beef calves.

Signs

- Afebrile course.
- Anorexia, abdominal pain, diarrhea.
- Death is rare if removed from contact with plant before becoming recumbent (cattle).
- Dehydration, lethargy, altered gait, weakness.
- Muscular tremors.
- Dark red urine.
- Incoordination, recumbency.
- May resemble vitamin E deficiency ("White Muscle Disease").
- Late fall, early winter.
- Acute form may resemble acute leptospirosis.
- Death in 5 - 7 days.
- In 26 beef calves poisoned by *C. occidentalis* findings included:
    - Anorexia, diarrhea.
    - Hyperpnea, tachycardia, progressive muscle incapacitation (associated with increased serum glutamate-oxaloacetate transaminase (GOT) and creatine phosphokinase (CPK) activities as well as myoglobinuria).
    - Death may occur within 24 hours after signs of acute illness and is almost assured in animals that become recumbent.

Lesions

- *C. occidentalis.*
    - Paleness of various skeletal muscles.
    - Microscopic myodegeneration.
    - Moderate hepatic centrilobular necrosis and fatty degeneration.
    - Acute renal tubular degeneration.
    - Generalized pulmonary edema.

- Cattle.
    - In 26 beef calves poisoned by *C. occidentalis* findings included:
        - Myocardial degeneration.
        - Congestive heart failure.
        - Widespread skeletal myodegeneration.
        - Muscles with characteristic transverse stippling.
        - Varying degrees of toxic hepatitis and nephritis.

Diagnosis

- Identification of *Cassia*, evidence of consumption, and appropriate clinical signs and lesions.
- Myodegeneration on microscopic examination.
- Increase in serum creatine phosphokinase (CPK), SGOT, LDH.
- Rule out poisoning due to ingestion of avocados, an ionophore, white snakeroot and gossypol.

Treatment

- Recovery usually follows removal from access to plant but an abnormal gait may remain for weeks.
- With acute myoglobinuria consider fluid therapy and bicarbonate.
- For hyperkalemia consider using insulin and glucose to drive K+ into cells.

Prevention

Cattle should not be allowed access to coffee senna especially when ample good forage is unavailable.

Note

- Poisoning is occasionally encountered in the USA.
- Used in human medicine as a cathartic.
- Useful model of a toxic myodegenerative disease.

Partridge Pea (*Cassia fasciculata* Michx.)

Family - Pea (Leguminosae).
Growth Form - Annual herb from fibrous roots.
Stems - Upright, branched, hairy or smooth, up to 2 feet tall.
Leaves - Alternate, divided into 20 - 30 leaflets narrowly oblong to lanceolate, rounded at the tip, but with a short point, tapering to the asymmetrical base, without teeth, hairy or smooth, up to 3/4 inch long.
Flower Arrangement - Flowers 2 - 4 from the axils of the leaves.
Flowers - Yellow, up to 1 1/2 inches across, borne on slenderstalks.
Sepals - 5, green, united below.
Petals - 5, yellow, 3 of them slightly smaller than the other 2.
Stamens - 10.
Pistils - Ovary superior.
Fruits - Pods narrow, flat, somewhat hairy, up to 2 1/2 inches long.
Habitat - Fields, prairies, roadsides, woods.
Range - Throughout the state.
Time of Flowering - July to September.
Associated Plants - Tall Tickseed (*Coreopsis tripteris*), milk spurge (*Euphorbia corollata*), switch grass (*Panicum virgatum*), and black-eyed Susan (*Rudbeckia hirta*).

Zigadenus - Death Camas

Zigadenus gramineus - Grassy death camas
Z. venenosus - Meadow death camas
Z. paniculatus - Foothill death camas
Z. nuttallii - Nut Fall's death camas
Z. densus
Z. elegans
Z. fremontii

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Other Plants that Affect the Heart
Most species	Hours	Days (?), often lethal; poisoning is infrequent	

Family - Liliaceae (Lily family)

Description

- *Zigadenus gramineus.*
    - Plant - Bulbous perennial, onion-like.
    - Stem - Tall, single, smooth.
    - Leaves - Narrow, grass-like, not stalked, up to 1 1/2 feet long.
    - Flower - Branched cluster of yellow-white to green-white flowers.
    - Root - Onion-like bulb but **no** onion aroma in leaves or bulbs.

Habitat

- *Z. gramineus.*

  Saskatchewan to Idaho, south to New Mexico and Utah.

- *Z. venenosus.*

  West Coast States east to southwestern Idaho, Western Utah, and most of Nevada. Canada south to Florida, Texas, New Mexico, Arizona and Canada.

- *Z. paniculatus.*
    - Largely in Great Basin, Utah, Nevada, Southern Idaho, Eastern Oregon, and Central Washington, plus small parts of adjacent Arizona, California, Wyoming, and Montana.
- *Z. nuttallii.*

    - Prairies of Eastern Kansas, Eastern Oklahoma, and Eastern Texas to south edge of Edwards Plateau.

Toxic Principle

Contains steroidal alkaloids such as zygacine which is similar to the nonteratogenic alkaloids of *Veratrum* spp.

Mechanism of Action

Cardiovascular effects of similar *Veratrum* alkaloids include lowering of blood pressure due to dilation of arterioles, constriction of venules and slowing of the heart rate.

Toxicity

- Seeds are most toxic.
- Young plants are more toxic than mature plants.
- Bulbs are less toxic than the leaves until flowering time.
- All parts are toxic, particularly the leaves and bulbs.
- Sheep.
    - One-half lb may cause poisoning.
    - Minimum lethal dose is 15 - 20 ounces (400 - 600 g/100 lb body weight).
    - Lethal dose ranges from 0.6 - 6% of BW.

Susceptible Species

- Sheep more susceptible than cattle, horses, chickens.
- Swine vomit quickly and generally do not get poisoned.

Signs

- Often just found dead.
- Signs appear from 1.5 hours to 8 hours after ingestion.
- Salivation.
- Retching, possibly vomiting, and abdominal pain.
- Increased respiration.
- Stiff legs.
- Hyperirritability.
- Muscular weakness, trembling and staggering.
- Weak, fast, irregular pulse.
- Dyspnea, cyanosis.
- Weakness, depression.
- Incoordination - Some recover.
- Convulsions may occur.
- Low temperature.
- Collapse, coma, death.
- Death occurs from within a few hours to 2 days.
- Mortality is high.

Lesions

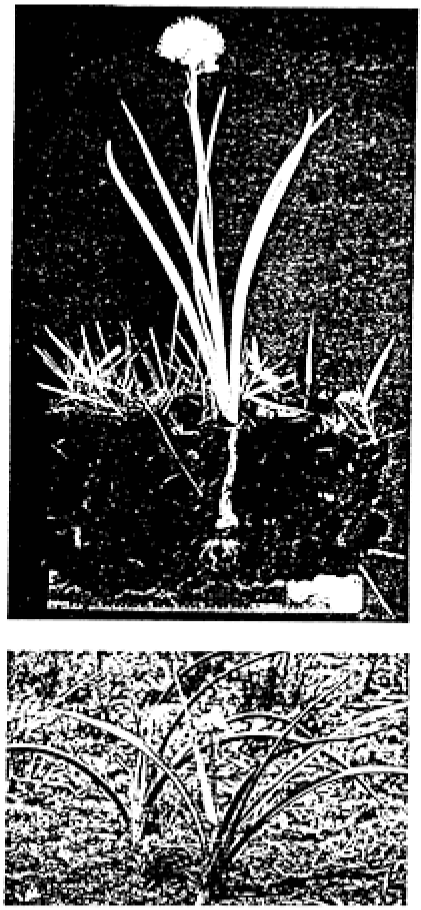
- Inflammation of GI tract.
- Congestion of lungs and kidney.
- Heart in systole.
- Degeneration of areas of skeletal muscles and myocardium may also be seen.

Diagnosis

Identification of *Zigadenus*, evidence of consumption, and accompanying clinical signs of toxicosis.

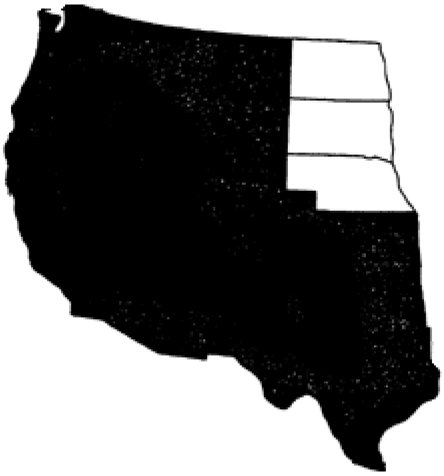
How it Affects Livestock

Deathcamas causes marked disturbance in respiration and heart action. A 100-pound sheep may die if it eats 1/2 to 2 pounds of green foliage. The amount of foliage that will cause an animal's death depends on the species of plant eaten. Severely poisoned animals usually die; those less seriously affected may recover.

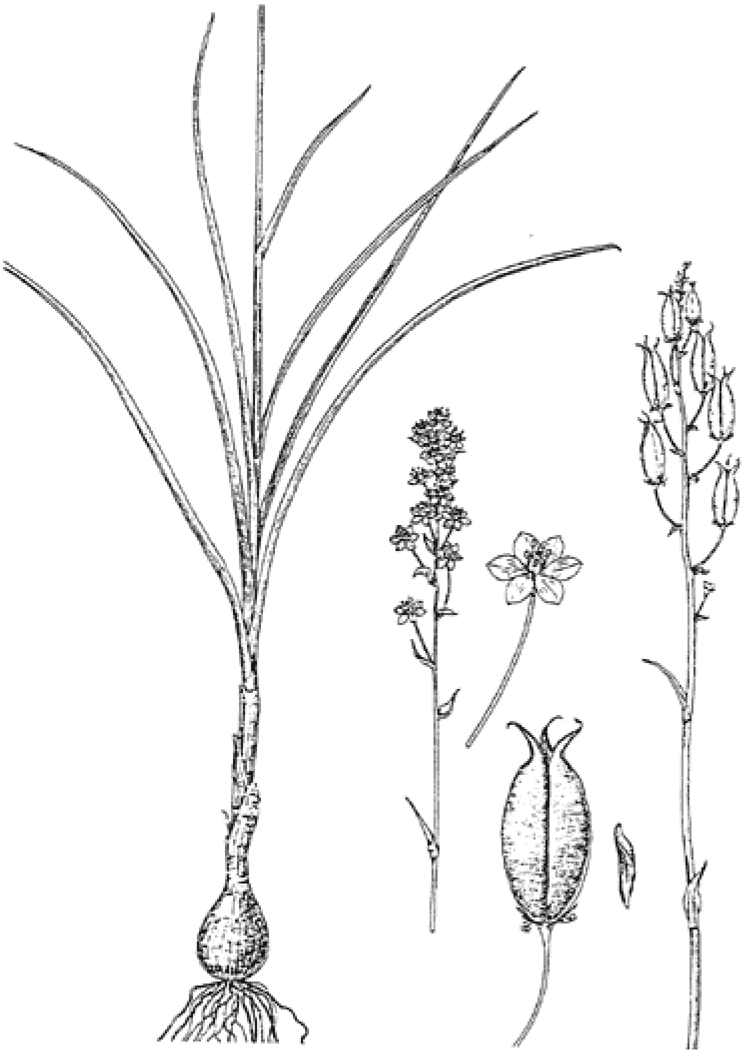


Deathcamas is a pernnial that produces grasslike leaves in groups of three from a deeply burled bulb. The plant may be 4 to 16 inches tall. Yellowish-white flowers grow in clusters atop the stalk. Top, meadow death-camas; bottom, foothill deathcamas.

Meadow deathcamas (yellow blossoms) growing in a grassy meadow, a typical habitat where its density often reaches levels that are hazardous to grazing animals.



Distribution of Deathcamas



Foothill Deathcamas - Note the long slender leaves, scaly bulb, delicate flowers, 3-celled seed pods, and seed (enlarged, lower right) of this deadly plant.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
Avocado (*Persea americana*) in cage birds	Caged birds, goats, other herbivores	12 hours to 2 days	Days; death usually occurs within 2 days of onset	Full Table for Other Plants that Affect the Heart
White snakeroot (*Eupatorium rugosum*) (See Toxicants that Cause CNS Depression)	Horse	Days to chronic	Permanent damage	
Jerusalem cherry (*Solanum pseudocapsicum*)	See Cholinergic Blockers			
Kleingrass (*Panicum*)	See Hepatogenous Photosensitizers			
False hellebore (*Veratrum californicum*)	(See Teratogens)			
Vitamin D-Containing Plants	(See Nephrotoxic Plants)			

(*Solanum malacoxylon* and *Cestrum diurnum*)		

- *White Snakeroot in the Horse (*Eupatorium rugosum*) (See Toxicants that Cause CNS Depression)
- Jerusalem Cherry (*Solanum pseudocapsicum*) (See Cholinergic Blockers)
- Kleingrass (*Panicum*) (See Toxicants that Affect the Skin)
- False Hellebore (*Veratrum californicum*) (See Teratogens)
- Avocado (*Persea americana*) in cage birds and other species (See Toxicants with Mixed Effects on the Central Nervous System)
- Vitamin D-Containing Plants (*Solanum malacoxylon* and *Cestrum diurnum*)

Organic Compounds that Affect the Heart

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Ionophore Feed Additives

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Organic Compounds that Affect the Heart
Monensin (Rumensin ®; Coban ®)	See Monensin section			
Lasalocid (Bovatec ®; Avatec ®)	See Lasalocid section			
Other ionophores	Most species	Hours to 2 days	Days to permanent damage; often lethal	

- Monensin, lasalocid, salinomycin, narasin, and laidlomycin propionate are ionophore feed additives and/or coccidiostats.
    - Horses are often poisoned, but cattle and other species also are affected.
    - Clinical pathology changes, arrhythmias, and heart lesions are highly variable with ionophore toxicoses in the horse, even in lethally affected animals.
- Salinomycin is reportedly quite toxic to turkeys.
- Recently salinomycin-contaminated commercial food seems to have caused a large outbreak of ascending paralysis leading to respiratory paralysis and deaths in domestic cats.
    - Affected cats might also exhibit histologic evidence of myelin degeneration.
    - It is suspected that the drug may have been in gut contents of poultry incorporated in the diet.

Monensin

(Rumensin ®, Coban ®)

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Organic Compounds that Affect the Heart
Most species	Hours to 2 days	Days to permanent damage; often lethal	

Sources

- Produced by *Streptomyces* fungi.
- Feed additive used in food producing animals.
- Beef cattle.

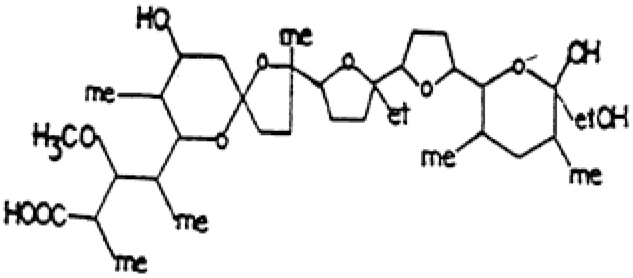
    Used to increase feed efficiency, control bloat, lactic acidosis, and to decrease the likelihood of acute bovine pulmonary emphysema and edema. Shifts volatile fatty acid production in rumen from acetic and butyric acids to propionic acid.

- Poultry.

    Coccidiostat.

- Research - To study movement of ions across cell membranes.

- Available forms - Premix, (Rumensin ®, Coban ®), intermediate mix, and ready to feed (final ration intended rates are 5 - 30 g/ton of feed).
- Not approved for sheep, swine, dairy cattle, or horses.



Molecular structure of monensin

Toxicity

Single dose oral LD_{50} in various species	
Species	**LD_{50}** (mg/kg)
Horse (most susceptible)	1 - 2
Sheep	11.9
Swine (approximate minimum lethal dose = 7 mg/kg)	16.8
Dog	> 20
Cattle	22 - 80 (varies)
Goat	26.4
Chicken (most resistant)	200

- Conditions surrounding exposure.
    - Improper mixing, settling (especially in liquid supplements).
    - Exposure of therapeutic doses for food animals to susceptible species.
    - Concentrate, intermediate mix may poison any of the species.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorption from GI tract is rapid.
- Rapidly metabolized by liver P450 enzymes in a significant first-pass effect - metabolites excreted via biliary system and feces.
- Inhibition of P450 by macrolide antibiotics from fermentation media (after removal of most of the drug) in the feed of cattle apparently decreased hepatic detoxification of monensin and thus resulted in monensin toxicosis.
- No urinary excretion.
- Does not accumulate in heart or skeletal muscles.
- Small fraction of ingested amount enters systemic circulation.

Mechanism of Action

- Lipid soluble, transports monovalent cations preferentially across cell membranes. It is very potent in transporting Na^+ across lipid membranes.
- Proton exchange for sodium, leading to acidosis and potassium loss.
- High intracellular sodium leads to secondary intracellular calcium overload.
- This leads to mitochondrial swelling, catecholamine release, and increased myocardial cell and diaphragm cell contractility.
- Finally, all of this leads to:
    - Early positive inotropy.
    - Later negative inotropy and contracture.

- Results include skeletal muscle and cardiac muscle dysfunction.
- Some renal and gastrointestinal effects.

Signs

- Vary slightly with species.
- Latent period varies with species and other host factors (age, diet, etc.) as well as dose ingested.
- Signs appear within 12 hours to up to 72 hours.
    - Anorexia, ataxia, diarrhea, sudden death-seen in most all species affected.
    - Sublethally affected animals may linger 8 days and recover.
    - Delayed deaths may occur long after the acute exposure and apparent recovery (cardiac fibrosis). Permanent cardiac damage is possible in sublethal cases.
    - Respiratory dyspnea.
    - Signs of general cardiovascular collapse, weakness, decreased exercise tolerance, cyanosis, recumbency and death.
    - Depression, ataxia, stiffness.
    - Shock.
    - Loose watery diarrhea - Colic in the horse (secondary floral changes/ rumenitis in cattle).
- Myoglobinuria - Sheep, swine and dogs.
- Renal tubular damage - Equine.
- Colic, sweating, sudden death, delayed deaths all seen in equine.
- EKG changes in the horse occur in some animals and may include marked S-T segment depression, atrial fibrillation, paroxysmal atrial tachycardia, and multiple ventricular extrasystoles of multifocal origin. Post-recovery EKG alterations may reflect cardiac fibrosis.
- EKG alterations in cattle in some cases include prolongation of Q-T interval and QRS complex, 1st degree heart block, occasional premature atrial beats, and increases in T wave amplitude.
- Death may occur during an acute toxic episode or weeks thereafter.

Clinical Pathology

- Hemoconcentration, shock - reflects cardiac - skeletal muscle damage.
- Calcium, sodium seldom altered.
- Elevated CPK, LDH, and AST.

Lesions

- Equine: Cardiac pathology (almost entirely).
    - Edema.
    - Pericardial and epicardial hemorrhages - generalized tigroid appearance to heart (pale streaking).
    - Sanguinous effusions in body cavities.
    - Histologic lesions of myocardial necrosis and secondary lesions associated with heart failure.
- Bovine: Similar to horse - cardiac pathology.
    - Rumenitis - mild.
    - Some skeletal muscle damage - myoglobinuria.
- Ovine: Mainly skeletal muscle lesions.
    - Pale streaks in skeletal muscle; histologically evident skeletal muscle necrosis.
    - Pulmonary edema.
    - Few cardiac lesions.
    - Diffuse gastrointestinal hemorrhages.
- Porcine: Mainly skeletal muscle lesions.
    - Bilateral, symmetrical, white dry areas of skeletal muscle.
    - Difficult to detect cardiac lesions in swine.

        When seen localized to left atrium only.

    - Severe myoglobinurias.
- Poultry:
    - Congestion of head, neck, liver, and lungs.
    - Sanguinous tracheal exudate.

    - Myocardial enlargement and pallor.
    - Hydropericardium.

Diagnosis

- Appropriate signs and postmortem lesions, EKG abnormalities.

  History of exposure.

- Rice hulls are often used as a carrier for monensin, lasalocid, and other feed-additive ionophores. Feed microscopy can, therefore, help suggest whether ionophore assays of feed are likely to be of value.
    - Analysis of feed samples, stomach/rumen contents (many labs will not test for ionophore antibiotics).
    - Tissue samples (e.g., liver, kidney) not very effective for detecting poisoning: Half-life of monensin is too short.

Treatment

- May be extended and involved.
- Poor prognosis if cardiac related signs are present due to possibility of permanent cardiac damage or just sudden death.
- Early cases: prevent further exposure, activated charcoal and a saline cathartic (if no diarrhea already present).
- Minimize stress.
- Life support - no specific antidote.
    - Fluids - large volumes for shock, bicarbonate as needed to correct acidosis.
    - Vitamin E/Selenium may help in swine perhaps in other species; more data needed.
    - Correct diagnosed cardiac irregularities if warranted. Avoid cardiac glycosides.
    - Routine treatment of rumenitis in cattle.
- Residue considerations.
    - Monensin does not accumulate in bovine tissues therefore no tolerance levels are set by FDA in this species - check with local officials.
    - Monensin is not cleared for use in egg laying birds.
    - **Not** used in dairy cattle.

Differential Diagnosis

White muscle disease, white snakeroot poisoning, lasalocid toxicosis, *Taxus* spp.

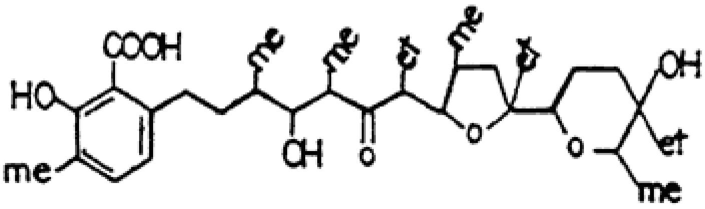
Lasalocid

(Bovatec ®; Avatec ®)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Heart
Most species	Hours to 2 days	Days to permanent damage; often lethal	

Sources

- Polyether antibiotic, ionophore.
- Produced by *Streptomyces* fungi.
- Feed additive for cattle rations to improve feed efficiency and rate of gain.
- Approved for prevention of coccidiosis in sheep.
- Anticoccidial agent in poultry rations.
- Available forms: Bovatec ® 68 Medicated Premix (68 gm of lasalocid/lb of premix).
- One lb of premix is added to 2,000 lb of feed to produce feed containing 34 mg/lb of mixed feed.
- Avatec ® Medicated Premix.



Molecular structure of lasalocid

Toxicity

Species	Acute LD_{50} mg/kg
Poultry	71.5
Mouse	146.0
Adult rat	122.0
Rabbit	40.0
Horse	21.5

Species	Toxic Dose
Cattle	A single oral dose of 100 - 125 mg/kg produced death in 6 - 10 days in 2 cattle.
Sheep	Toxic in a single oral dose of 12 mg/kg BW or 6 daily oral doses of 8 mg/kg BW.
Swine	Fed 58 mg/kg BW, death occurred in 1 day
Donkey	57.5 mg/kg caused death in 1 donkey. "All donkeys" given 47.5 mg/kg survived.
Canine	20 - 30 mg/kg (varies)

Mechanism of Action

- Believed to be due to ionophoric properties. Lasalocid transports monovalent cations preferentially and it also transports catecholamines.
- Ion selectivity: transports Ca^{++} > Mg^{++} (among divalent cations) and K^+ > Na^+ (among monovalent cations).

Absorption, Distribution, Metabolism and Excretion (ADME)

- See Monensin.
- Reduced lasalocid metabolism by chloramphenicol, an inhibitor of P450 enzymes was associated with delayed neurotoxicity in broilers.

Clinical Signs

- Similar to monensin.
- Cattle.
  - At a single oral dose of 10 - 25 mg/kg, cattle were anorectic for 3 days.
  - A single oral dose of 25 mg/kg resulted in depression and anorexia with diarrhea occurring from 2 - 5 days postdosing. At 50 mg/kg, slight muscular tremors in the flank were also noted starting 6 - 9 hours postdosing. In addition, animals had increased rates of respiration. Doses above this resulted in similar, though more severe, clinical signs. At 125 mg/kg, death occurred on day 10 (6).
- Horses.

  Horses given over 18 mg/kg showed reduced activity, ataxia, paresis, and complete or partial anorexia. Clinical signs lasted 2 - 8 days in animals given sublethal doses (5).

- Swine.

  Above 35 mg/kg has produced transient muscular weakness (1).

- Other species.

  Not reported.

- Dogs experience paresis or paralysis with retention of the ability to wag the tail and move the eyes. In the late stages of the toxicosis, death results from apparent respiratory paralysis.

Clinical Pathology

- Cattle - Increased CPK, LDH, SD.
- Horses - Increased glucose, phosphorus, total bilirubin, LDH. Of these, total bilirubin is likely to be the most consistently observed abnormality.
- Other species - Not reported.

Lesions

- Equine - Congested lungs, hyperemic kidneys, petechial hemorrhages to epicardium.
- Cattle - Myocardial and skeletal muscle vacuolation; myocardial contraction bands.
- Sheep - Necrosis more severe in skeletal than cardiac muscle.
- Deer - Myocardial necrosis.
- Lesions in dogs were so mild as to be difficult to distinguish from normal.
- Other species - Not reported.

Diagnosis

- Rice hulls are often used as a carrier for lasalocid, monensin, and other feed-additive ionophores, as well as vitamin and mineral supplements. Therefore, feed microscopy can help suggest whether ionophore assays are likely to be of value.
- Suspect feed or rumen/stomach contents can be analyzed for lasalocid.
- Low tissue levels, like monensin. No withdrawal period needed for cattle, chickens, or sheep fed at recommended levels.

Treatment

- See Monensin. No specific antidote.
- Activated charcoal, intravenous fluids, supportive care.

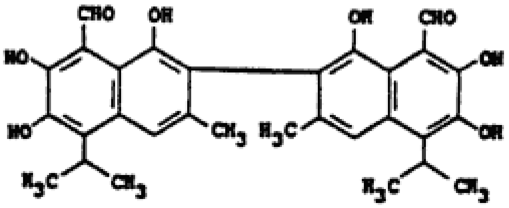
Cotton (*Gossypium* spp.), Cottonseed, and Gossypol

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Heart
Gossypol (constituent of cottonseed and cotton seed meal)	Swine, calves, horses, dogs, poultry	Weeks to a year	Weeks to permanent damage; often lethal	

Gossypol (*Gossypium* spp. - cotton plants) - Members of the Malvaceae.

Sources

- Cottonseed, cottonseed meal, and cottonseed cake are high protein materials used in animal feeds. Cottonseed contains about 20% protein and 20% oil. The meal made from it contains about 40% protein and 7% or less oil. Cottonseeds contain a polyphenolic binaphthalene pigment called gossypol in the glands of the seeds which appear as tiny black spots. Most gossypol is removed during processing of the seeds. Several commercial processes have proven less than trustworthy in producing cottonseed meal of consistently low gossypol content.
- The toxic substance in cottonseed, gossypol, is present only in the pigment glands which are retained in the seed after decortication (hull removal). Pigment glands of this type are present only in cottonseed and a few closely related plants of the Malvaeceae. The pigment glands contain approximately 50% gossypol, which accounts for 2 - 5% of the weight of the seed and is comprised of 3 isomeric forms. Gossypol is also associated with 2 other pigments, gossypurpurin and gossyverdurin; the latter being more toxic than gossypol itself and possibly responsible in part for the finding that gossypol content may not always account for the entire spectrum of effects occurring in cottonseed related toxicosis. The gossypol content of cottonseed varies considerably with the strain of cottonseed, the location in which it is grown, the particular climatic conditions that year, and on the extraction procedure.
- The pigment glands may be removed from the seed by flotation. Alternatively the gossypol may be inactivated by heating but this procedure results in binding of the gossypol to lysine which reduces the nutritive value of the protein present. The cellulose walls of the pigment glands are quite tough and although gossypol is soluble in a number of solvents and reactive with a variety of compounds, it is not extractable nor does it react in most milling or rolling processes unless the glands are first ruptured. This is accomplished by the addition of water which ruptures the seams of the seeds.
- With the traditional cottonseed-oil extraction, the seed is heated to relatively high temperatures for comparatively long periods of time before mechanical pressing to expel the oil. During this cooking, the majority of the pigment glands are ruptured and their contents released into the meal. Free (toxic) gossypol is inactivated (bound) to form a nontoxic molecule in time by reactions which occur in the meal spontaneously or during the milling process. The amount of free gossypol present in the meal is dependent upon the degree to which the glands have ruptured and the degree of subsequent inactivation of the gossypol.
- With care and attention to moisture content during cooking, commercial press extraction meals can attain a constant free gossypol average of near 0.02%.
- Delinted cottonseed, sometimes referred to as "delinted cotton" or "whole cotton", may be made by treating cottonseed with sulfuric acid. This treatment may impart a yellow color to the dark seeds. Delinted cottonseed is sometimes added to cattle diets.



Gossypol

Fate and Mechanisms of Action

- Gossypol is highly lipid soluble. Primarily eliminated via feces; minor amount leaves as a conjugate in the urine. In rats, gossypol is relatively slowly eliminated: 97% is eliminated in 19 days.
- Cottonseed meal associated impairment of growth and hypoprothrombinemia may be, in part, attributable to inhibition of protein synthesis. Anemia may result from the chelation of iron to gossypol. Gossypol also binds to proteins and amino acids rendering them unavailable during the digestive process. It has also been suggested that gossypol may interfere with oxidative processes and prevent the release of oxygen by hemoglobin.
- It is believed that the major effects of gossypol on the liver are secondary to heart failure.
- Undecorticated cottonseed meal or cottonseed cake contains up to 25% indigestible fiber which may cause trouble from intestinal impaction. Cottonseed meal is so low in vitamin A that a deficiency may occur in animals unless adequately supplemented. Cattle with blindness, ataxia, swollen joints and anorexia may sometimes respond to vitamin A.

- Gossypol has been demonstrated to inhibit testicular lactic dehydrogenase (LDH) enzymes via a competitive inhibition of a cofactor required for LDH activation. Gossypol has been investigated as a possible human male contraceptive agent.

$$\text{Lactate} + \text{NAD}^+ \xrightarrow{\text{LDH}} \text{Pyruvate} + \text{NADH} + \text{H}^+$$

LDH function

- Gossypol accumulates in the liver and inhibits glutathione S-transferase (may therefore decrease detoxification of other xenobiotics).

Toxicity

The acute toxicity of gossypol is low with the LD_{50} being on the order of 5 gm/kg. However, the ingestion of small amounts over long periods of time leads to illness and death.

Susceptible Species

- The horse is relatively resistant, but, in general, monogastrics are usually readily poisoned.
- Dogs and swine are affected by gossypol and rabbits and guinea pigs are also quite sensitive.
- Ruminants are not usually very susceptible except young calves before the rumen is fully functional. In fact, adult ruminants have been known to consume significant quantities of cottonseed meal containing free gossypol without effect. The resistance of adult ruminants has been attributed to the binding of gossypol to soluble proteins in the rumen to form a nontoxic molecule which resists subsequent digestion. When young Holstein and Jersey calves were fed cottonseed meal from birth, the Holsteins were much more sensitive and the signs and lesions were similar to those occurring in swine.
- **Broiler Diets** - Tolerance to gossypol may be affected by age and strain of birds, level of dietary protein, iron salts, and alkaline materials. Lysine and methionine are the two amino acids that are most likely to be marginal in cottonseed meal (CSM)-containing broiler rations. Broiler performance is not affected by dietary-free gossypol levels up to 100 to 150 ppm (0.010 - 0.015%). Levels up to approximately 400 ppm (0.04%) may be fed successfully if ferrous sulfate is added at 1:1 iron to free gossypol weight ratio.
- Experimental results showed that laying hens could tolerate free gossypol at up to 440 mg/kg diet without any significant adverse effect on egg production, egg weight, feed intake, and feed conversion efficiency. Supplementation of diets containing free gossypol with $FeS0_4$ did not improve egg production, egg weight, and feed conversion efficiency. Free gossypol at 140 mg/kg feed had no effect on color of egg yolk or egg white in fresh eggs but caused discoloration in eggs stored for 1 month or longer. $FeSO_4$ at 120 or 240 mg/kg feed increased the tolerance to free gossypol to 280 mg/kg feed and slightly decreased the occurrence of discoloration in stored eggs.
- In hens rate of egg production, egg weight, interior egg quality and feed intake were not significantly depressed by diets with free gossypol up to 200 mg/kg. But more than 50 mg/kg produced an increasing number of objectionable olive-colored yolks. The addition of ferrous sulfate at iron:gossypol ratios 4:1 and 8:1 was fairly effective in eliminating the number of objectionable eggs when free gossypol concentrations were as high as 100 mg/kg, but iron was less effective at higher gossypol intakes.
- Chickens were fed diets containing different concentrations of free gossypol and iron sulfate for 17 days. In some trials, chickens were given gossypol 0 or 980 mg/kg diet and Fe at 1,000, 1,500, 2,000, or 3,000 mg/kg. It was concluded that growing chickens can tolerate free gossypol at up to 590 mg/kg without any significant adverse effect on body weight gain, feed intake or feed conversion efficiency. $FeSO_4$ was only partly effective in alleviating the adverse effects of high concentrations of free gossypol on performance.
- **Layers** - Excessive gossypol has been shown to affect weight gain, feed intake and efficiency, mortality, egg production, weight, quality, and hatchability. Dark discoloration of egg yolks presents a serious economic problem and results from an interaction between gossypol and iron in the yolks. Actual egg production, however, is not affected by dietary-free gossypol at up to 200 ppm (0.02%). Dietary concentrations of free gossypol up to 40 to 50 ppm may be fed without consequential egg yolk discoloration. When higher levels of free gossypol are fed (up to 150 ppm), protection against yolk discoloration can be provided by supplementing with iron in a 4:1 weight ratio to gossypol.

Signs

- Gossypol has a cumulative effect. Poisoning usually appears abruptly, but signs tend to begin after the animals have been on cottonseed meal for 4 weeks to as much as a year.
- Clinical signs in growing pigs receiving low concentrations of gossypol include inappetence weight loss, and poor feed conversion.
- Larger amounts cause weakness, dyspnea, emaciation, generalized edema and death. Generally death occurs 2 - 6 days after the onset, but on occasion the signs may persist for a month before death.
- The most prominent signs in affected swine are respiratory and include dyspnea, gasping or thumping, and occasionally there may be froth or bloody froth at the mouth.
- The rate of gain is somewhat inconsistently affected. Emaciation and weakness may appear with other signs, but feed intake is sometimes maintained until shortly before death.
- Cyanosis may be noted immediately prior to death.
- Dogs very sensitive to antifertility effects. Antifertility effects in swine not determined.
- Some people become hypokalemic.
- Poultry, which are of intermediate sensitivity, develop weight loss, anorexia, decreased hatchability, discolored egg yolks and whites and abnormal texture of the egg whites.
- (See Susceptible Species section above.)

Lesions

- Gross lesions consist of widespread congestion and edema, the result in significant measure of progressive congestive heart failure.
- Large quantities of straw-colored fluid are usually present in the peritoneal, pericardial, and thoracic cavities.
- The ventral body wall, lungs, kidneys, mesenteric l.n. and other organs are sometimes congested and/or swollen.
- The lungs are edematous and there is usually foam in the trachea and sometimes pneumonia is present.
- Irritation or ulceration of the gastrointestinal tract may occur when gossypol is present at high concentrations.
- The liver appears congested and may be somewhat degenerative, however, severe changes are often present histologically.
- In many lobules most hepatocytes are lost leaving a thin zone of intact cells in the periphery with replacement of the lost cells by hemorrhage.
- Areas of the skeletal muscle appear white and the heart is edematous, flabby, dilated, and on histologic section, areas of necrosis are present. In long standing cases, regenerative hypertrophy may be present.

Diagnosis and Differential Diagnoses

- Quantification of free gossypol in the feed and characteristic lesions.
- Differentials - Hepatosis dietetica, mulberry heart disease (selenium deficiency), coal tar poisoning (phenolics), selenium toxicity, monensin, lasalocid poisoning.

Treatment

- Management of gossypol toxicosis may be comprised of efforts to alleviate pulmonary edema and congestive heart failure.
- Withdrawal of cottonseed from the diet is indicated as is supplementation with vitamin A.
- If unaffected animals in the group are to continue on cottonseed containing diets, supplementation with vitamin A, iron, lysine and protein are recommended.

Prevention

- The toxicity of gossypol may be almost completely neutralized by the addition of iron, in the form of ferrous sulfate to the diet at a rate of 1 part iron to 1 part gossypol.
- The relative efficacy of dietary iron in an effort to limit adverse effects of gossypol on poultry are discussed under Susceptible Species above.
- Nevertheless, for unspecified reasons, this method has not been widely accepted.

- At a consistent average gossypol concentration of 0.02%, swine rations may safely contain up to 25% cottonseed meal.
- Generally, for swine and poultry, the concentration of gossypol in the diet must be less than 0.01% to be safe.
- According to Kingsbury, a general rule, based on the usual concentration in commercial meal, is that cottonseed meal may be added to swine feeds at a level of 9% without danger.
- High protein intake is protective against the effects of gossypol. Deaths in swine were produced at a free gossypol concentration of 0.02% in the diet when the protein content of the ration was 15%; however, when the protein content of the ration was 30%, no deaths occurred even when the diet contained 0.03% gossypol.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Heart
Urea and other non-protein nitrogen sources	(See Toxicants with Mixed Effects on the CNS)			
Xylazine	Most species	Minutes to hours	Hours; rarely lethal	
Amitraz	(See Toxicants that Cause CNS Depression)			
Caffeine and other methylxanthines	(See Toxicants Associated with Central Nervous Stimulation or Seizures)			
Tricyclic Antidepressants	(See Toxicants with Mixed Effects on the Nervous System)			
Cocaine	(See Toxicants Associated with Stimulation or Seizures)			
Diphemanil methyl sulfate **(Diathal ®) and Anesthetics**	-	-	-	
Blister Beetles	(See Toxicants that Affect the Kidneys)			
Cyclopiazonic acid (Mycotoxin) (rare)	-	-	-	
Citreoviridin (Mycotoxin) (rare)	-	-	-	
Moniliformin (Mycotoxin) (toxicoses may be rare, but furhter research seems to be warranted on potential occurence)	-	-	-	
Batrachotoxin in poison dart frogs Central and South America (*Dendrobates* and *Phyllobates*) (causes sodium channels to stay open without related changes in potassium or calcium. Also causes a massive release of acetylcholine in nerve-muscle preparations. Cause of death seems to be due to severe cardiac arrhythmias and cardiac arrest.)	-	-	-	

- Blister Beetles (See Toxicants that Affect the Kidneys)
- Urea (See Toxicants with Mixed Effects on the CNS)
- Tricyclic Antidepressants (See Toxicants with Mixed Effects on the Nervous System)
- Cocaine (See Toxicants Associated with Stimulation or Seizures)
- Diphemanil methyl sulfate (Diathal ®) and Anesthetics

- Cyclopiazonic acid (Mycotoxin) (Unlikely)
- Citreoviridin (Mycotoxin) (Unlikely)
- Moniliformin (Mycotoxin)
- Amitraz (See Toxicants that Cause CNS Depression)
- Xylazine (See Diagnosis and Management Section, under Emetics)

Section XV: Toxicants that Affect the Lungs

Inorganic Compounds that Affect the Lungs

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Direct Effects on the Lungs

Toxicants that selectively affect the lungs include gaseous and small particulate compounds and mixtures that are able to bypass the scrubbing capabilities of the upper respiratory tract, trachea and larger bronchi. Included in many agents associated with work place hazards such as mineral dust (pneumoconiosis), coal dust (anthracosis or anthracosilicosis [blacklung]), silica (silicosis) asbestosis (asbestosis), cotton dust (byssinosis), sugar cane dust (bagassosis), coliform bacteria (asthma and other respiratory problems in some workers), nitrogen oxides (silo filler's disease), as well as tobacco smoke (emphysema, bronchogenic carcinoma). Also included are low molecular hydrocarbons such as kerosene, gasoline, light crude oil, and mineral seal oil that tend to be aspirated into the lungs during and shortly after ingestion.

A few toxicants, such as the herbicide parathion are selectively taken by the lung. In addition parathion is bioactivated by lung P450 in Clara cells of the lung which results in toxicity. Several other agents bioactivated by lung P450s that have a furan ring and cause acute bovine pulmonary edema and emphysema include the amino acid tryptophan (in corn and lush pastures), perilla ketone in the purple mint plant (*Perilla futescens*) and the mycotoxin ipomeanol produced by the mold *Fusarium solani* on sweet potatoes (*Ipomea batatas*).

Indirect Effects on the Lungs

A range of other toxicants affect the lungs by altering bronchial smooth muscle tone or secretions. The cholinesterase-inhibitors are of major importance as they often affect lung function in this way and they may also depress respiratory drive from the medulla and potentially cause paralysis of the muscles of respiration. All of these are the result of the buildups of excess acetylcholine.
Hemorrhage is another problem sometimes caused by toxicants, and it may cause pulmonary failure when bleeding into the lung is involved.
Many compounds that affect the action of the heart may secondarily result in pulmonary edema and/or compensatory tachypnea either of which might initially suggest a potential primary lung effect.
Compounds that cause severe hypoproteinemia may affect the hygroscopic pressure of the blood to the point that pulmonary edema may become more likely.
Anemia, carboxyhemoglobinemia, or methemoglobinemia related to a number of etiologies may reduce the oxygen-carrying capacity of the blood resulting in respiratory compensation.

Inhaled Toxicants and Respiratory Tract Dosimetry

Definitions related to inhalation of particulate toxic substances -
Deposition - Implies removal of particles from inhaled air because of impact with and retention by an airway surface
Clearance - Implies elimination of deposited particles from their initial deposition site
Retention - Pertains to quantity of particles that remain in the respiratory tract at a particular time after exposure.

Retention = Deposition - Clearance

Particle deposition is influenced by features of the particle and the host.

- Particle features include: size, shape, density, electrical charge, and hygroscopicity.
- Host features include: aspects of the respiratory tract anatomy, breathing rate, and breathing pattern.
- Airway branching points are major sites of particle impact and, therefore, deposition.
- In dogs, larger particles (greater than 1 μ m) are deposited mainly in the upper respiratory tract. Approximately 10 - 15% of smaller particles are deposited in the tracheobronchial tree; and approximately 20 to 30% are deposited in the alveolar region.

- With regard to clearance, the assumption is that the most rapidly cleared particles are those that were deposited in the tracheobronchial region.
- Particulate toxicants deposited in the anterior nasal passage may move to the exterior, but most of the material deposited in the nasal area overall is likely to be swallowed.
- Similarly, particles deposited in the tracheobronchial tree tend to be moved by the "mucociliary escalator" to the pharynx where they are swallowed.

Tracheobronchial mucociliary clearance is influenced by:

- **Age** - The rate increases from childhood to adulthood and then may decline as the animal grows older.
- **Exercise** - May increase rate.
- **Disease** - Certain lung diseases decreased rate (e.g., respiratory infection, asthma, chronic bronchitis).
- Deposited particles that are retained may be phagocytized by alveolar macrophages.
- If the particles penetrate through the epithelial cells they may be phagocytized by interstitial macrophages.
- Solubilized poisons able to penetrate the epithelium may react with local calls or may be cleared via the blood or lymph.
- Dog pulmonary macrophages seem to patrol a smaller region than the pulmonary macrophage of rodents and even humans. Also, clearance of insoluble and slowly soluble particles from the dog lung to the lymph nodes is slower than in rats and mice.

Nitrogen Oxides (Silo Filler's Disease)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Inorganic Compounds that Affect the Lungs
Most species	Minutes to hours	Hours to permanent damage, potentially lethal	

Sources

- Nitrogen dioxide is formed when nitric oxide in fresh silage comes in contact with oxygen in the air.
- Toxicosis is primarily seen when people (and sometimes animals) are near silos shortly after they are filled. The risk is highest when feedstuffs are high in nitrates (drought years), since in the ensiling process these form nitric acid as the silage reacts with oxygen in the air.
- Gas production is greatest in alfalfa silage, reaching a peak in 24 hours and apparently ending in 2 or 3 days. Concentrations as great as 1500 ppm can be reached during the first 48 hours after filling a silo.
- Nitrogen dioxide usually is seen as a yellowish-brown haze if any amount of it has been formed. Other toxic by-products such as NO or N_2O_4 are colorless and odorless.
- This gas has an irritating odor similar to laundry bleach. It is heavier than air and therefore remains in the silo below the upper edge of the last door or settles down through the chute to the silo room and into the barn.
- Oxides of nitrogen play a very important role in air pollution because in urban areas, large quantities of these oxides are constantly being generated from such sources as automobiles, diesel engines, thermal power plants, boilers, industrial gaseous wastes, etc.
- Combustion of x-ray films results in the production of nitrogen dioxide.
- Plastic plants also have the potential of giving off this gas.
- Exposure to nitrogen tetroxide in the missile industry can produce symptoms identical to those from nitrogen dioxide and should be treated in a similar fashion.

Mechanism of Action

- Nitrogen dioxide dissolves in water to form a mixture of nitric and nitrous acids, both of which are very irritating and corrosive to the mucous membranes. Due to its relatively low solubility in water, however, the transient passage of nitrogen dioxide through the upper respiratory tract may not cause significant signs but may result in considerable damage to the lower respiratory tract, where the duration of contact and the amount of moisture are greater.
- The acid is only slowly absorbed and removed from the lung. The ultimate effect is one of local irritation which results in pulmonary edema. Because of a short residency time, the upper airways are generally

less affected. Prior exposure can produce a degree of tolerance to subsequent inhalation of comparatively high concentrations of nitrogen oxides.

- NO_2 also acts by causing lipid peroxidation, which is maximal at 24 hours after exposure and lasts at least 24 hours thereafter. Vitamin E deficiency increases susceptibility to nitrogen dioxide. Nitrogen dioxides, in turn, increase the susceptibility to infection by decreasing the ability of the lung to remove pathogenic microorganisms.

Toxicity

- "Silo-filler's disease", or silage gas poisoning, also called bronchiolitis fibrosa obliterans due to inhalation of nitrogen dioxide, is especially hazardous for agricultural workers.
- Inhalation of low concentrations of the oxides of nitrogen may cause little or no discomfort of the upper respiratory tract but may result in death hours later due to pulmonary edema. A brief exposure to 200 ppm can be fatal.
- Though it is an invisible gas in smaller concentrations, it is still dangerous. Humans are able to detect NO_2 at levels as low as 0.1 - 0.2 ppm in the air.
- In laboratory animals, a short exposure to only 0.5 ppm of nitrogen dioxide for 4 hours leads to histologic alterations. These mild lesions are reversible.
- In humans exposed for 10 minutes to 5 ppm of nitrogen dioxide, there was a 92% increase in airway resistance, and this response was delayed until 30 minutes after exposure.
- When laboratory animals were exposed for 2 hours to 50 ppm nitrogen dioxide, pulmonary edema occurred. Even after 1 hour exposure to only 1 ppm, there were alterations in the configuration of collagen and elastin.

Signs

- The clinical manifestations vary according to the intensity of exposure and the period of inhalation.
- In man, the clinical features and chest x-rays of this condition closely resemble sarcoidosis, miliary tuberculosis, histoplasmosis, etc.
- Inhalation of nitrogen dioxide can produce serious respiratory symptoms with feeling of suffocation in the chest, dyspnea, cyanosis, syncope, pulmonary edema and death.
- An increase in respiratory rate, a decrease in compliance and an increase in airway resistance occurs.

Lesions

- Extent of pathological changes in the lungs corresponds to the degree of exposure.
- Cyanosis.
- Pulmonary mast cells are ruptured, and degranulated and the alveoli become markedly expanded.
- Pulmonary congestion, edema.
- Emphysema.

Diagnosis

KI starch papers are available commercially--turn dark when exposed to NO_2 gas.

Treatment

- Treatment consists of immediate administration of oxygen and artificial respiration if necessary.
- Corticosteroids have been found very effective in relieving the pulmonary edema and symptoms.
- Additional supportive care includes controlling pulmonary edema and administering broad-spectrum antibiotics for bronchopneumonia.
- Recovery may require from 1 - 6 months. Some emphysematous changes may persist indefinitely.

Prevention

- Education of the farmer to the dangers of toxic silo gas, as well as the safety measures that should be carried out to prevent undue exposure and inhalation by both humans and animals, is paramount in the elimination of this serious type of poisoning.

- This hazard of farming can be avoided simply by not entering a silo during filling and for a week or 10 days after completion thereof. Animals should not be allowed to gather in a barn near the base of a silo shortly after filling.

Gaseous Ammonia

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Inorganic Compounds that Affect the Lungs
Most species	Minutes to chronic	Hours to permanent damage due to infection (usually upper respiratory), rarely lethal	

Sources

- This section deals primarily with the local effects of inhaled ammonia as a result of its release from decaying animal wastes.
- Although hydrogen sulfide is probably responsible for more acute deaths in animals in confinement, ammonia is the toxic air pollutant most frequently present in high concentrations in animal facilities.
- Ammonia is present especially when animals are held in an area in which feces and other wastes are allowed to accumulate and decompose on a solid floor.
- Concentrations increase due to agitation of manure. Ammonia is lighter than air, and will rise from a manure pit or pack.
- Usually concentrations in enclosed animal facilities remain below 30 ppm when ventilation systems are operational, but it is not unusual to find 50 ppm or higher in spite of normal function of these systems.
- Anhydrous ammonia gas, commonly used from compressed gas tanks, is a potentially dangerous source for animals and especially man. Because of the pressure involved, breakage of hoses, failure of valves or human error when transferring ammonia from dealer tanks (nurse-tanks) to farmer tanks can result in a serious degree of exposure.

Structure of Ammonia

NH_3.

Mechanism of Action

- Ammonia is highly soluble in water. As a result, ammonia tends to go into solution in the aqueous layer on the surface of the eye and upper airways, resulting in irritation in these areas.
- Ammonia may irritate the respiratory mucosa from the nose to the lungs, depending upon the concentration present and the time of exposure.
- At concentrations usually found in animal environments (less than 100 ppm), the primary mechanism is chronic stress on the respiratory tract as a result of the continual irritation.

Toxicity

- Humans can detect the pungent odor at about 10 ppm.
- Signs are seen primarily when birds are exposed to 75 - 100 ppm or more.

Signs

- Shallow breathing, excessive lacrimation, clear or purulent nasal discharge, reduced production.
- Chickens on deep litter may exhibit keratoconjunctivitis, corneal opacity and tracheitis. They may keep their eyes closed most of the time, become listless and eat less than normal.
- An increase in secondary respiratory infections, including an increase in severity of atrophic rhinitis may occur in ammonia exposed animals. In one study, the prevalence of the lesion was unaffected despite increased severity of lesions in the affected animals.
- Poultry may often experience corneal opacity which may correlate with listlessness and reduced feed intake, perhaps a result of blindness.

- Permanent loss or impairment of eyesight, respiratory problems and skin burns result from exposure to anhydrous ammonia. The material should be handled only by persons wearing tight fitting goggles. When exposure has occurred, first aid is comprised of continuous irrigation of the exposed surface with water for 15 - 20 minutes.

Lesions

- Because of the high solubility of ammonia, when lesions occur, they tend to be present in the eyes and upper air passages.
- Apart from the keratitis, corneal opacities and tracheitis in chickens and the increased severity of atrophic rhinitis in swine, the lesions associated with ammonia are usually mild and usually confined to the upper respiratory tract.
    - Increased secretion of mucus in the respiratory tract.
    - Hyperplasia of the bronchiolar and alveolar epithelium has been reported.

Overheated Polytetrafluoroethylene - Teflon or Silverstone

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Inorganic Compounds that Affect the Lungs
Caged birds	Minutes to hours	Hours to permanent damage, highly lethal	

Sources

- Polytetrafluoroethylene is a synthetic polymer used to make Teflon ® and Silverstone ® non-stick cookware. When pans or skillets are left on a range and become overheated (above 280ºC or 530ºF) pyrolysis products capable of causing toxic effects are produced. Empty PTFE cookware on burner set on high can reach > 750ºF. A recently developed product is PTFE coated drip pans, which can be dangerous to birds under conditions of normal usage. The temperature of the drip pan can exceed 650º F after 5 minutes if the burner is on high and > 1,000ºF after 10 minutes.
- The polymer coating is known to break down forming, in the process, particulates and acidic volatile gasses. Toxicoses have been reproduced in birds exposed to air from a pan heated to 400ºC.
- Some heat lamps may have a Teflon coating which may break down with excessive heat.

Toxic Principle

- Toxic breakdown products in heated Teflon or Silverstone include the following:
    - Carbonyl fluoride.*
    - Perfluoroisobutylene.*
    - Hexafluorocyclobutylene.*
    - Carbon tetrafluoride (CF_4).
    - Hydrofluoric acid.
    - Monomeric tetrafluoroethylene.

Toxicity

- Acute, severe toxicosis occurs in pet birds.
- Mice and guinea pigs tolerated fumes lethal to birds.
- In humans, the condition is known as polymer fume fever and is comprised of a well-documented, transient flu-like syndrome.

Signs

- In birds, including cockatiels, parrots, budgerigars and finches as well as quail, the condition is generally a rapidly fatal one.
- Signs include acute pulmonary distress with noisy respiration and dyspnea.

- These signs are shortly followed by "rocking movements", eyelid blinking sometimes described as somnolence and agonal convulsions (in some cases), followed by death.

Lesions

- Extensive pulmonary hemorrhage and congestion.
- Particles may be seen in some lung sections.
- Particles similar to those found on air filters in the contaminated enclosure have been found in the lungs of affected birds. It is believed that the toxic effects arise as a result of the combined actions of toxic constituents carried on these particles and the acidic gasses (also) produced.

Differential Diagnosis

Carbon monoxide, methane, other toxic gasses. Acute pneumonia if a single bird is involved.

Treatment

- Birds often found dead.
- Remove from further exposure.
- Symptomatic care - steroids, warm humid environment, fluids, antibiotics if bronchopneumonia is present.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Inorganic Compounds that Affect the Lungs
High Doses of Selenium and Selenium Containing Plants (Acute)	See Metals and Metalloids that Affect the Skin			
Hydrochloric acid (HCl)	All species	Minutes to hours	Hours to 2 days, potentially lethal	
Hydrofluoric acid (HF)	All species	Minutes to hours	Hours, poisoning very rare	
Zinc phosphide (rodenticide) or aluminum phosphide (fumigant and general biocide)	See Toxicants Associated with CNS Stimulation or Seizures			

Organic Compounds that Affect the Lungs

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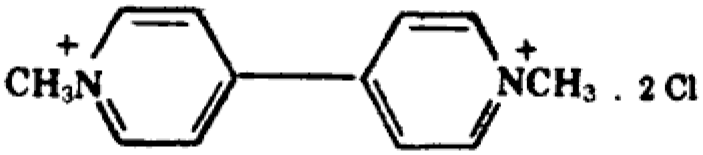
Paraquat (A Dipyridyl Herbicide)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Lungs
Most species	Hours to days	Days to permanent damage, often lethal	

Sources

- Paraquat is a dipyridyl herbicide which is applied at low application rates such as 1/2 lb/acre which is generally low enough that animals exposed to treated fields are not at risk of acute toxicosis.
- Problems arise, however, as a result of exposure to the concentrate or from ingestion of solutions of the chemical, not yet applied.
- Paraquat is a nonselective herbicide, causing a fast acting, contact kill on treated plants.
- Paraquat is used as a herbicide in no-till or minimum tillage programs.
- It is also used as a desiccant to remove the herbage prior to the harvest of soybeans, potatoes, melons and fruit from trees, as well as for other similar applications.
- Paraquat can be used on aquatic weeds and it apparently has a low toxicity to fish.
- Forage would possibly serve as a source of toxic amounts of paraquat if treated at extremely high rates since solutions as strong as 20% are sometimes prepared.
- A spray can has been available for spot treatment of weeds in residential yards.
- Paraquat has been used for malicious poisoning of dogs.

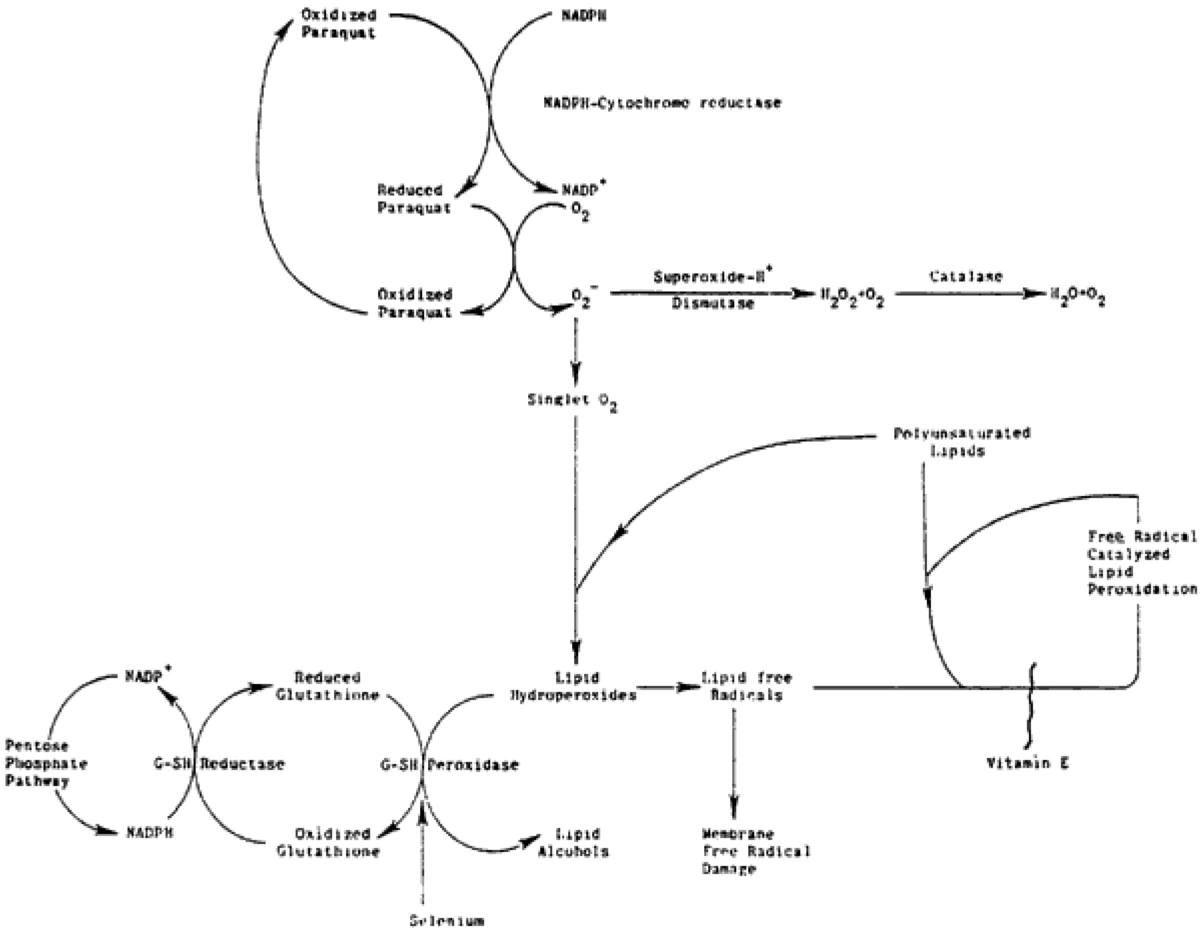


Absorption, Distribution, Metabolism and Excretion (ADME)

- Paraquat accumulates in the lungs until about 10 times the concentration of other tissues is reached.
- About 20% of orally ingested paraquat is absorbed. Even less is absorbed when applied topically.
- Most of the paraquat is excreted unchanged in the urine although some is metabolized and approximately 15% of the absorbed paraquat leaves in the feces. Passage of paraquat in milk is low (0.015%).

Mechanism of Action

- Paraquat is a very reactive compound, and the compound readily accepts an electron to become a paraquat free radical.
- When the paraquat free radical is reoxidized by loss of the electron it previously had accepted, a superoxide free radical is formed instead.
- This superoxide free radical is unstable and spontaneously breaks down to the reactive, singlet oxygen.
- Singlet oxygen, in turn, reacts with lipid membranes to form lipid hydroperoxides.
- Lipid peroxidation then continues in the lung in the same manner as it does in the liver after initiation by carbon tetrachloride, leading to membrane destruction and dysfunction with subsequent cell death.



Proposed mechanism of action for the *in vivo* toxicity of paraquat in which paraquat is reduced by microsomal NADPH-cytochrome reductase.

Toxicity

Species	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)
Rat	100	80 - 90
Cat	35	
Dog	25 - 50	
Turkey	290	500
Rabbit	50 - 150	350
Sheep	50 - 75	
Pig	25 - 50	
Man	4 - 40	
Cattle	35 - 50	

- Oral LD_{50}s range from 25 - 150 mg/kg BW. This can be compared to 1/2 - 1 lb per acre which translates to 3.5 - 7 mg/kg in grazing animal.
- Paraquat binds tightly to clay soils and, while such binding tends to decrease the availability and therefore the toxicity of a range of pesticides, it also tends to enhance the persistence of the chemical.

- Paraquat not bound to soil photodegrades rapidly. For example, approximately 50% is degraded in sunlight within 3 weeks.

Signs

- Apparently dogs and cattle have been poisoned more often than other domestic species (more reports of toxicoses in these species).
- Because of the time involved in the toxification of paraquat in the body, there is a delay after exposure of several hours up to 3 days prior to the onset of signs.
- If large amounts of paraquat are ingested, acute clinical signs may be seen, including excitation, ataxia, diarrhea, respiratory distress, and convulsions.
- Surfaces contacted by paraquat may be irritated or even ulcerated.
- In dogs, the onset of clinical signs is typically 1 - 3 days after exposure.
- Initial signs in dogs include vomiting and depression, as well as dehydration.
- Respiratory signs usually begin 2 - 7 days after the exposure and include tachypnea, dyspnea, moist rales and cyanosis. Gasping and death can occur within 8 days.
- Pneumomediastinum occasionally occurs as a result of the respiratory distress.
- The most troubling aspect of paraquat toxicosis is the progressive pulmonary damage that may continue to develop over a period of 7 or as many as 21 days.
- Initial pulmonary effects are dose dependent. Some animals die from pulmonary edema, while others survive only to develop severe pulmonary fibrosis a week or more thereafter.
- Paraquat toxicosis in cattle may first be noticed 1 - 3 days after exposure (ingestion). Anorexia, depression and diarrhea may occur and respiratory signs are somewhat less prevalent than in dogs.

Lesions

- Dark congested and hemorrhagic lungs with multiple areas of atelectasis.
- Bronchioles and alveoli may be dilated, and bullous emphysema may be present.
- In chronically affected animals, the lungs may be shrunken and fibrotic.
- There is also intraalveolar hemorrhage and edema.
- Necrosis is seen in the bronchiolar and alveolar epithelium, especially in the Type I alveolar pneumocytes.
- Progressive fibrosis in alveolar and interstitial tissues may result in significant pulmonary insufficiency.
- Paraquat toxicosis can also cause renal proximal tubular degeneration and focal centrizonal hepatic degeneration.

Diagnosis

- Analysis of the suspected source with detection of potentially toxic amounts.
- Analysis of urine may confirm exposure rather than necessarily establishing a diagnosis. With appropriate history and clinical signs and lesions, however, a diagnosis can be made.
- It has been suggested that lung or even muscle may be worth analyzing in selected cases.
- Because of rapid excretion, urine may be analyzed in many cases but would be of most value for only the first 2 days or so after exposure.
- Gross and histologic changes are important in the diagnosis of paraquat toxicosis.
- A rapid chemical screening test involves reacting 1 ml urine with 1 ml of 1% sodium dithionite in sodium hydroxide forming a blue-green color if positive (also cross reacts with diquat).

Treatment

- Rapid removal and adsorption of the ingested paraquat is the most important aspect of treatment.
- Because of the high affinity of paraquat for clays, it is widely known that bentonite or Fuller's earth is the preferred adsorbent for the herbicide.
- When these agents are not **immediately** available, however, it would be preferable to use activated charcoal immediately rather than waiting until the clay is available. Oral administration of ground clay kitty litter may serve as a worthwhile absorbent.
- A saline (magnesium or sodium sulfate) cathartic or an osmotic (sorbitol) cathartic should be given in every case, when animals are presented after recent exposure (i.e., last 12 hours or so).
- Forced diuresis and peritoneal dialysis may be used in selected cases, but care must be taken to avoid aggravating pulmonary edema.

- Agents which have been shown to be of benefit in paraquat toxicosis experimentally include niacin, riboflavin, ascorbic acid, superoxide dismutase (enzyme) (one form of superoxide dismutase is also known as orgotein = Pallosein ®), and N-acetyl-cysteine (mucomyst).
- Oxygen is contraindicated due to the possibility of aggravating oxidative injury to the lung.
- Clients should be made aware, early on, of the possibly grave prognosis in many cases. Some animals will, however, recover and detoxification efforts are worthwhile.

Note

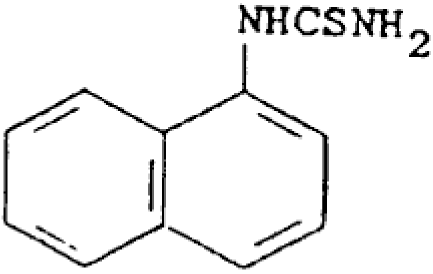
Diquat differs from paraquat in that the former does **not** cause significant pulmonary problems and, instead, tends to cause cerebral hemorrhage, lethargy, coma, and renal failure.

Alpha-Naphthyl Thiourea (ANTU)

Major Species	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Organic Compounds that Affect the Lungs
Dogs, cats	6 - 12 hours	Days, highltly lethal	

Sources

- Alpha-naphthyl thiourea is a fine gray insoluble powder possessing almost no odor or taste.
- The compound is extremely stable and does not deteriorate on prolonged storage.
- It finds primary use as a rodenticide and in doses less than 100 mg/kg has been found to be toxic only to the Norway rat, cats, dogs, mice and pigs.
- Usually baits are prepared by including 2% ANTU in cereals, meats or bread mashes.
- Baits containing ANTU are readily accepted by animals, but they are able to develop a tolerance towards the substance.
- ANTU is only rarely used at the present time.



ANTU
a-(1-Naphthyl)-2-thiourea

Toxicity

Dogs are the domestic species most often poisoned with ANTU. The LD_{50} is influenced by species and age. Comparative LD_{50}s of ANTU in mature animals are presented in the following table.

Species	**Route of Administration**	LD, mg/kg Body Weight
Norway rat, wild	Oral	6.9 ± .05
Dog	Oral	38
Mouse	Oral	19
Guinea pig	Oral	143
Cat	Oral	75 - 100
Pig	Oral	25 - 50

- Aged dogs are more susceptible to ANTU poisoning than young ones.
- An identical effect of age has been demonstrated in wild rats; suckling rats were 5 - 7 times more resistant to the effects of ANTU than old rats.
- The route of administering ANTU influences its toxicity in the dog and cat because emesis often occurs following oral administration.

Mechanism of Action

ANTU kills by producing a marked hydrothorax and pulmonary edema. The animal literally drowns in its own fluids. The accumulation of fluids is due to an increase in the permeability of capillaries in the lungs. When lymph flow from the lungs was monitored following the administration of ANTU to dogs, increases were noted within 90 minutes following dosing. At the eighth hour after dosing, the lymph flow had increased to 80 times its original value. The exact mechanism resulting in increased capillary permeability has not been determined. Reaction of ANTU with sulfhydryl groups may be a necessary part of the mechanism of toxic action, since it has been reported that sulfhydryl group blocking agents are effective antidotes in rats in some experimental conditions.

Signs

- Vomiting is one of the first signs noted, occurring a few minutes to a few hours following ingestion of ANTU.
- Breathing becomes rapid (short, jerky inspirations) and a shallow hacking cough may be noted. Moist rales can be detected in the lung fields.
- The extremities are cold to the touch and the visible mucous membranes appear cyanotic. The peripheral pulse is almost imperceptible while the cardiac impulse is accelerated and weak.
- Normal or subnormal temperatures are the rule in poisoned animals.
- Animals continue to vomit as the disease progresses and the vomitus may consist entirely of blood.
- A watery fluid diarrhea becomes hemorrhagic if the patient survives the acute symptoms.
- The affected animal remains standing or sits on its haunches to relieve thoracic pressure. As the animals become weaker, they assume a position of sternal recumbency.
- In the terminal stages, the lungs are congested or filled with fluid and fluid may escape from the mouth.
- The animal becomes comatose and fails to respond to external stimuli. Most deaths occur in 2 - 4 hours after symptoms appear. If the animal survives for 12 hours after ANTU exposure, the prognosis becomes more favorable.

Lesions

- The most apparent change noted at necropsy is hydrothorax. The thoracic cavity is often completely filled with a clear, colorless fluid. Severe edema of the lungs is a consistent finding and, in some instances, fluid will actually flow from the trachea when the lungs are removed from their cavity.
- The poison is moderately irritating to the stomach and intestines, and catarrhal inflammation is usually present in these organs.
- In many instances, the kidneys assume a blood red color as a result of intense hyperemia or congestion.

Diagnosis

Since chemical tests for ANTU are usually inconclusive, diagnosis is dependent upon history, characteristic clinical signs and necropsy findings.

Treatment

Emetics such as apomorphine (in the dog) may be of value if animals are presented early in the course of the poisoning and if the ingestion of baits containing ANTU is suspected. Because of the seriousness of ANTU toxicosis, measures to eliminate the gastrointestinal tract contents should be followed as soon as possible after exposure. Activated charcoal may possibly be of value in the lavage solutions and should be left in the lumen thereafter. If a thorough enterogastric lavage is not performed, then a saline cathartic should also be administered. Some authors suggest that mineral oil fats can enhance absorption of ANTU and should be avoided. Although silicone aerosols may prevent foaming of excessive bronchial fluids, there is no specific treatment for ANTU poisoning. Experimental evidence indicates that providing thiol groups may reduce mortality. Potential thiol-containing compounds include N-amyl mercaptan, N-acetyl cysteine, or thyacetyl cysteine. Atropine has not been helpful in controlling the pulmonary edema. The prognosis for animals suffering from clinically significant ANTU poisoning is poor.

Crude Oil, Petroleum Distillate Poisoning

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Organic Compounds that Affect the Lungs
Crude Oil	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal	
Kerosene	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal	
Diesel fuel	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal	
Gasoline and other light weight petroleum distillates (hydrocarbons)	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal	

Introduction

Crude oil or petroleum distillate poisoning of animals is a well-recognized clinical entity, but its pathogenesis remains poorly defined. The pollution of grazing areas with crude oil is relatively commonplace, and in areas supporting crude oil production, many livestock owners immediately suspect crude oil poisoning when livestock health is compromised. When animals sicken or die in areas contaminated with crude oil, producers and oil pipeline companies are often faced with damage suits seeking payments for livestock **allegedly** poisoned by crude oil. In general, cattle are the domestic species most commonly poisoned by exposure to crude oil or petroleum products, but poisoning has also been reported in sheep and horses. It is important to remember that livestock may be exposed to a variety of toxicants from the petroleum industry which must be differentiated from crude oil poisoning, including heavy metals, saltwater, caustic chemicals, glycols, and alcohols. Small and large animals are commonly exposed to paint thinner, gasoline, kerosene, motor oil, grease, and numerous other petroleum distillates. Often petroleum distillates are present in insecticidal preparations.

Source

- Crude oil toxicosis in cattle and sheep is most commonly related to leaks in oil pumping or transmission systems. Road oil and open fuel containers are sources of exposure to petroleum distillates.
- Cattle normally avoid oil spills, but feeder calves seem to be attracted to crude oil and will often drink several gallons of the material. Water or salt deprivation in animals may contribute to their consumption of crude oil.
- Petroleum distillates are mixtures of aliphatic (or saturated linear hydrocarbons) and aromatic (benzene ring containing) compounds. Some petroleum distillate fractions in order of decreasing volatility include benzene, gasoline, mineral spirits, kerosene, fuel oil (naphtha), lubricating oil, grease, paraffin wax, and asphalt/tar.
- Owners also use kerosene and other petroleum products in the treatment of a variety of disease conditions in their animals.

Toxicity

- The toxicity of crude oil appears to be related to its aspiration hazard and its irritant activity on pulmonary tissue. This correlates with the content of light hydrocarbon fractions (e.g., gasoline, naphtha, kerosene). Highly viscous oils are seldom aspirated.

- A 40 - 90% reduction in feed intake was noted when cattle were administered a single, oral 200 ml dose of kerosene or light petroleum solvent.
- Calves bloated immediately when administered 38 ml/kg BW of light, volatile crude oil. Less volatile oils produce bloat only at higher doses.
- Aspiration of stomach contents occurred in calves within 1 hour of being given a light, volatile crude oil at a dose of 40 ml/kg BW.
- When multiple doses of oil were given to calves over a 7-day period, the minimum total dosages resulting in aspiration pneumonia were 48 ml/kg, 56 ml/kg, and 74 ml/kg for light volatile (sweet) crude, kerosene, and heavy volatile (sour) crude oil, respectively.
- Kerosene is more damaging to the skin than crude oils.

Signs

- Odor of oil may be detectible on the breath, feces, urine, milk, and blood samples.
- **Nervous system**:
    - Anorexia, mild depression.
    - Excitability, depression, shivering, head tremors.
    - Incoordination, mydriasis, tonic-clonic convulsions.
- **Digestive system**:
    - Regurgitation of oil; oil may be seen on lips and muzzle.
    - Vomiting may be seen with highly volatile crude oils.
    - Dry stool with ingestion of more volatile crude oil, diarrhea with less volatile crude oils; bloat with either.
- **Respiratory system** (aspiration pneumonia; usually the most life-threatening aspect of the toxicosis):
    - Coughing, rapid shallow respiration.
    - Increased heart rate.
    - Reluctance to move, weakness.
    - Oil-stained nasal discharge.
- Hyperemia, thickening, and in severe cases fissuring of the skin have occurred following a single topical application of crude oil or kerosene to the body surface of calves.
- Similarly, ewes treated with diesel fuel as a vehicle for an insecticide experienced severe skin and wool sloughing.

Clinical Pathology

- Decreased blood glucose due to prolonged anorexia.
- Pneumonia associated:
    - Hemoconcentration.
    - Initial leukopenia followed by leukocytosis (neutrophilia).

Lesions

- Lesions of aspiration pneumonia are the most common necropsy finding, and these may be accompanied by localized pleuritis and hydrothorax. The apical, cardiac, diaphragmatic and intermediate lobes of both lungs are usually dark purple, consolidated, and may contain multiple abscesses. Raised yellow-green plaques may be found in the ventral tracheal mucosa. Encapsulated pulmonary abscesses may be found in cattle surviving for an extended period of time. Oil may or may not be grossly visible in pulmonary tissue.
- Oil may not be visible in the rumen of cattle that die more than 4 days after ingestion of oil.

Diagnosis

- The history, clinical signs, and postmortem changes are of primary importance in establishing a diagnosis.
- Rumen contents may be mixed with warm water (1:1) to ascertain the presence of crude oil or kerosene. Any oil or kerosene present in rumen contents will float on the surface.
- Ample quantities of rumen contents, feces, and lung tissue should be submitted for chemical analysis, as well as any spilled oil, contaminated water, or forage. These samples should be carefully protected from cross-contamination during necropsy then sealed in a jar and packed in ice.

- Careful documentation of all observations is imperative owing to the possibility of subsequent legal action. It is impossible to have too much information and supportive evidence when involved in legal proceedings.

Treatment

- Although the removal of oil from the rumen would theoretically be of benefit, such measures are seldom undertaken, since any procedure that increases the risk of aspiration is contraindicated.
- Rumenotomy with replacement of a specimen of rumen contents from a normal animal is indicated in cases of large hydrocarbon ingestions.
- In cases where rumenotomy is not feasible, the careful administration of vegetable oil (500 - 1000 ml) by nasogastric tube has been recommended to reduce the hazard of aspiration by increasing the viscosity of the oil mixture. This should be followed by a saline cathartic.
- Glucose IV may be indicated in those animals with prolonged anorexia.
- Antibiotic therapy should be reserved for animals exhibiting evidence of bacterial pneumonia.
- In small animals, monitoring for pulmonary effusions may be of value. If due to edema, positive end expiratory pressure may be of value. If due to bacterial pneumonia, antibiotics are indicated. Corticosteroids are **contraindicated** except when life-threatening circulatory shock is present.
- Removal of oil from the haircoats or feathers can be accomplished by repeated washing using Dawn liquid dishwashing detergent followed by a creme rinse and additional water rinses.

Ethylenediamine Dihydroiodide (EDDI)

Iodine compounds, such as ethylenediamine dihydroiodide (EDDI)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Lungs
Most species	Hours to chronic	Days, rarely lethal	

(Note for more complete discussion see *Clinical and Diagnostic Veterinary Toxicology*, 3rd ed., pages 145 - 151).

Sources

EDDI or ethylenediamine dihydroiodide is used as a feed additive at low levels to prevent foot rot in cattle and to prevent soft tissue lumpy jaw in cattle and sheep. High levels are used to treat existing foot rot or soft tissue lumpy jaw in cattle and as an expectorant for respiratory infections in cattle, swine and poultry.

Signs and Lesions

- EDDI has a wide margin of safety and toxicoses are infrequent.
- The primary toxic effect is an intermittent, nonproductive cough.
- With increased duration or degree of exposure, other systems are affected, primarily the skin, joints and eyes.
- For example: after 30 days of exposure to excessive EDDI, calves developed thickened skin, rough hair, sloughing of the superficial epidermis and alopecia. These lesions were present, especially over the neck and back and around the eyes. Eventually, a joint related lameness develops in some EDDI-poisoned cattle.

Pennyroyal Oil - Ketone Pulegone

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Lungs
Cats, dogs	Hours	Hours to days, potentially lethal	

Each year the Illinois Animal Poison Information Center receives a few calls regarding pennyroyal oil, an aromatic oil sometimes used as an insecticide on small animals.

Signs and Lesions

- The calls regarding suspected or assured toxicosis consistently involve cats, and callers describe panting, dyspnea or exaggerated bronchial sounds.
- These respiratory effects are compatible with reports of pennyroyal oil toxicosis in humans, the effects of which may also include disseminated intravascular coagulation, hepatic necrosis, abortion and death.

Treatment

- No specific therapy is known.
- Thorough bathing in a liquid dish detergent is necessary to terminate absorption of that portion of the agent still on the surface of the skin. Note: If a dermal or subcutaneous depot occurs in pennyroyal oil toxicosis, as takes place with some other toxicants, absorption into the systemic circulation may continue even after bathing.
- N-acetyl cysteine (Mucomyst ®) has been used experimentally in humans to protect the liver from damage.
- See information on Petroleum Distillates.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Organic Compounds that Affect the Lungs
Smoke Inhalation	All species	Minutes to hours	Hours to permanent damage, highly lethal	
Organophosphorus or Carbamate Insecticides	See Inhibitors of Cholinesterase			
Freon (fluorocarbons, chlorofluorocarbons)	Small animals	Minutes to hours	Hours days, potentially lethal, poisoning is rare	
Formaldehyde	All species	Minutes to chronic	Days, potentially lethal	
Fumonisins	See Toxicants with Mixed Effects on the CNS			

Plants and Mycotoxins that Affect the Lungs

- Rapeseed or Forage (*Brassica*) (See Goitrogenic Toxicants)
- 3-Nitro-containing Locoweeds (*Astragalus* and *Oxytropis*) (Some species of these plants cause emphysema in sheep) (See Toxicants with Mixed Effects on the CNS)
- *3-Substituted Furans and Acute Bovine Pulmonary Edema and Emphysema
  - Purple Mint (*Perilla frutescens*) (perilla ketone)
  - Corn (*Zea mays*) (tryptophan)
  - Lush Pastures (tryptophan)
  - Mycotoxin 4-Ipomeanol in Moldy Sweet Potatoes (*Ipomea batatas*) infected by the fungus *Fusarium solani*
- Fumonisins (See Toxicants with Mixed Effects on the CNS)

Section XVI: Toxicants that Cause Asphyxia

Toxicants that Cause Asphyxia

V. Beasley

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Toxic Gases Overview

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Asphyxia
Carbon dioxide	All species	Minutes to hours	Minutes to hours; often lethal	
Helium	All species	Minutes to hours	Hours; poisoning is rare	
Hydrogen (also flammable)	All species	Minutes to hours	Hours; poisoning is rare	
Aliphatic hydrocarbons (also explosive!; e.g. methane, ethane in natural gas)	All species	Minutes to hours	Hours; poisoning is rare	
Nitrogen oxides	(See Inorganic Compounds that Affect the Lungs)			
Hydrogen sulfide	(See Toxicants that Cause Primarily Respiratory Paralysis)			

General Considerations

The air livestock breathe is frequently contaminated with potential toxicants. Usually these gases are dissipated and diluted by the normal environmental air movement. However, in today's modern confinement-rearing buildings, adequate ventilation of the animals' surroundings is often dependent upon propermechanical function of systems intended to move air and proper management including that of ventilation systems by the producer. When one or both of these components is faulty, problems can arise.

Sources

- Urinary and fecal decomposition and respiratory elimination.
  - Ammonia, hydrogen sulfide, methane, carbon dioxide.
  - Other gases released in minute amounts.
  - Note gaseous ammonia discussed in Inorganic Compounds that Affect the Lungs.
- Improperly adjusted or vented fuel-burning heaters.
  - Carbon monoxide, carbon dioxide.
- Fermentation of nitrogenous compounds, especially plants.
  - Nitrogen oxides.
- Usually, even at the low ventilation rates used during the winter months the concentration of these gases remain low. However, poor facility design, accidents, or improper operational procedures can produce high concentrations quite rapidly.
- In acute toxicosis, clinical signs are dramatic, ranging from pronounced dyspnea to sudden death. In chronic poisoning, effects may be more subtle and may include: lethargy, dyspnea, anorexia, decreased growth, lacrimation, salivation, decreased resistance to certain infectious diseases, and increased incidence of stillbirths.
- Guidelines for estimating gas concentrations may be found in: Clinical and Diagnostic Veterinary Medicine; 3rd ed. pp 365-367. Concentrations can be measured with easy-to-use colorimetric indicator tubes which are available commercially.
- Gas concentrations are usually expressed as ppm but may be expressed as mg/L.

Nitrogen Dioxide (NO_2) (also see section on Nitrogen Oxides)

- Yellowish brown; bleach-like smell.
- **Heavier than air**.
- Primary source is fermentation of ensiled forages; "silo-filler's disease".
- Formed during first 2 weeks after silage is cut and stored.
- Highest concentrations in first 48 hours.
- Human nose can detect very low concentrations.
- 5 ppm has caused lesions in lab animals - concentrations in silo gas may exceed 100 ppm.

Signs

- Forms nitric acid when combines with H_2O on respiratory mucosa - permanent lung damage.
- May die instantly or hours, days, or months later.
- Dyspnea, salivation, coughing, methemoglobinemia.
- On necropsy, severe pulmonary edema, "dark red" kidneys, hemorrhage, and bronchiolitis may be seen. Emphysema may occur in chronic cases.
- No specific treatment; even fresh air has no direct beneficial effect other than removing the source of the problem.

Hydrogen Sulfide (H_2S)

- Refer to notes in section: "Toxicants Primarily Causing Respiratory Paralysis".
- Rotten egg smell.
- **Heavier than air**.
- Produced by bacterial action on sulfur-containing amino acids and other sources of sulfur.
- Note - Rapidly paralyzes olfactory nerves at high concentrations.
- Death from respiratory paralysis.

Methane (CH_4)

- Colorless, odorless.
- **Lighter than air**.
- Produced by bacterial decomposition of carbonaceous materials such as excreta.
- Not notably toxic; biologically inert.
- Would need 90% methane to deprive of O_2.
- Principle danger lies in its flammability and explosiveness.

Carbon Dioxide (CO_2)

- Odorless.
- **Heavier than air**, therefore collects in lower areas of buildings.
- Present in normal atmospheric air at 300 ppm.
- Can cause "suffocation" in overcrowded, inadequately ventilated enclosures.

Sources

- Normal respiration of animals.
- Improperly vented (though properly adjusted) fuel-burning heaters.
- Freezing or birds' nests may block vent openings.
- Decomposing excreta.
- Rarely approaches dangerous levels.

Toxicity and Signs

When concentrations exceed 400,000 ppm, may see anxiety, staggering, coma, cyanosis, and death.

Lesions

Dark tissues and blood.

Treatment

Provide fresh air, artificial respiration if needed.

Prevention

Maintenance of proper humidity in winter and proper temperature in summer helps to keep CO_2 in confinement buildings within acceptable levels.

Note

It has been suggested that if all ventilation were stopped in an air-tight building, animals would generally die from hyperthermia before CO_2 toxicosis.

Carbon Monoxide (CO)

- Odorless, colorless, slightly lighter than air.
- **Note** - See also Smoke Inhalation section that follows this one.

Sources

- Background concentrations in air range from 0.02 ppm (fresh air) to 40 ppm (high traffic area).
- Incomplete combustion of hydrocarbon fuels (inadequate oxygen to form CO_2).
- Improperly adjusted or vented heaters in confinement buildings.
    - Higher fuel costs have resulted in an effort to reduce ventilation in winter to cut fuel costs.
    - Often fresh air vents are covered or flue pipes get blocked (birds' nests, etc.).
- **Note** - Some persons feel that Elbee white heaters are notorious for CO problems.
- Exhaust fumes of internal combustion engines.
    - Dogs in trunks of cars with faulty exhaust system, or in enclosed garages have been affected.
    - Metabolite of methylene chloride (dichloromethane).

Mechanisms of Action

- Competes with O_2 for binding sites on several proteins including hemoglobin (Hb).
    - Affinity of Hb for CO = 250X that for O_2.
- When CO is bound to Hb, its affinity for O_2 molecules already bound increases (oxygen-dissociation curve shifted to the left). This prevents release of that O_2 to tissues. Net result is tissue hypoxia.
- Fetal Hb of man has a greater affinity for CO and O_2 than does adult Hb. In cats, dogs, and pigs, the fetal hemoglobin is the same as maternal, but the fetal blood cells have lower amounts of 2,3-diphosphoglycerate (2,3-DPG) which enables the fetus to take up O_2 from the dam. Regardless of the species involved, it appears likely that the fetal blood carboxyhemoglobin (COHb) may be higher than that of adult in the same environment. In pigs, the frequency of stillbirth increased significantly when maternal COHb concentrations were greater than 23% saturation of hemoglobin. The COHb concentrations in Caesarian section-delivered pigs were 3 - 22% greater than maternal blood concentrations. In sheep, fetal COHb concentrations were 58% greater than maternal concentrations.
- Amount of blood COHb depends on:
    - The rate of formation of COHb - is proportional to the atmospheric carbon monoxide concentration.
    - The disappearance half-life of COHb - approximately 2 hours.

Toxicity and Signs

- Relationship between exposure to onset of clinical signs.

Atmospheric CO	Time to clinical effect (30% COHb)
1200 ppm	1 hour
600 ppm	2 hours
400 ppm	4 hours
200 ppm	infinite

- High exposures may produce rapid deaths.
- Lower exposures produce drowsiness, incoordination, dyspnea, and coma.
- Relationship of blood carboxyhemoglobin to clinical manifestations:

% blood COHb	Effects
1 - 3	None
6 - 8	Decreased ability to maintain attention
20	Definite psychomotor disturbance
20 - 40	Lethargy, disturbance in gait, EEG changes
60 - 70	Death

- High concentrations in farrowing houses will increase the incidence of stillborn piglets. Greater than 250 ppm CO in swine farrowing houses is capable of increasing the number of stillbirths. Near term sows may deliver dead piglets 12 - 48 hours after introduction to a farrowing barn which has elevated CO concentrations.
- Possible permanent deafness in small animals (rare).

Lesions

- Characteristic cherry-red blood.
- Pink or red coloration of tissues and nonpigmented skin.
- Sometimes see bronchial dilation and distension of major blood vessels.

Histopathology

- Necrosis of cortex and focal leukoencephalomalacia in the white matter of the cerebral hemispheres, the globus pallidus, and brain stem (whether such lesions are likely to be detectable in very many clinical cases is disputed by some pathologists).
- There may also be glial-vascular proliferation, edema, and hemorrhage in the brain.
- Demyelination.
- Brain lesions may coincide with permanent deafness in dogs and cats.

Diagnosis

- History.
- Measurement of CO in air.
- Measure COHb in blood. COHb is stable for several days if the blood is refrigerated.
  - Local hospital laboratories can often run a COHb test: send reference sample from an unexposed animal of same species.
- COHb greater than 2% in fetal thoracic fluid.
- Fetal heart blood may range from 20 - 60% COHb; sows' blood may be greater than 10% COHb.

Treatment

- Fresh air.
- **Best** treatment is 90 - 95% O_2 with 5 - 10% CO_2.

Section XVII: Toxicants that Inhibit the Function of Cytochromes

Toxicants that Inhibit the Function of Cytochromes

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Cyanide

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Inhibit the Function of Cytochromes
Cyanide hydrogen cyanide = prussic acid, calcium cyanide, sodium cyanide, cyanide in some smokes	All species	Minutes to hours	Hours; extremely lethal	
Wild black cherry (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Chokeberry (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Plum (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Peach (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Sudan grass and other *Sorghum* spp. [Cyanogenic glycoside-containing plant] (See Methemoglobin Producers)	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Arrowgrass (*Triglochin*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
White clover (*Trifolium*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal (unlikely cause of toxicosis)	

Cyanide or prussic acid (HCN) toxicosis is a serious and often deadly problem which primarily results when animals are exposed to cyanogenic plants. High levels of exposure usually result in death. Cyanide is infrequently used as a fumigant rodenticide.

Sources

- Cyanogenic plants. Cyanogenic means having the ability to produce cyanide from cyanogenic glycosides.
    - Wild black cherry, chokecherry, plum and peach, all of which are *Prunus* spp; especially in seeds. Cherry wood chips may be made with leaves and fresh chips of fresh green wood which may contain potentially toxic amounts of cyanogenic glycosides.
    - Amygdalin, a cyanogenic glycoside and a constituent of Laetrile, a purported anticancer drug.
    - Sudan, sorghum and Johnson grass, all of which are *Sorghum* spp.
    - Arrowgrass (*Triglochin*).

    - White clover (*Trifolium album*).
- Note, the sorghum plants much more often cause nitrate toxicosis (See Methemoglobin Producers).
- Photographic solutions.
- Some silver and metal polishes.
- Industrial chemicals.
- HCN is used as fumigant rodenticide.
- Has been used as a gaseous agent to execute humans.
- **Note -** Methylisocyanate, the gas released from the chemical plant used to produce carbaryl in Bhopal, India, acted primarily as an extreme irritant rather than as cyanide itself.

Production

- Normally cyanogenic glycosides are spatially separated from beta-glycosidase in the intact plant.
- When combined, a multi-step reaction produces HCN.

Factors Favoring Production

- High nitrogen/low phosphorus soils.
- Young plants.
    - Cyanide content decreases rapidly after pollination.
- Leaves and seeds contain more cyanide-releasing potential than stalks.
- Spraying with herbicide.
- Freezing.
- Plant injury or stunting.
- Mastication and digestion (especially in the rumen).

Mechanism of Action

- Classical theory:
    - Cyanide ion reacts with Fe^{+3} (ferric) ion of cytochrome oxidase to form a stable complex.
    - Conversion of Fe^{+3} to Fe^{+2} is thereby prevented so that electron transport and cellular respiration are stopped. The blood is oxygenated, but cannot be utilized by the cells.
    - The lack of O_2 utilization in chemoreceptors and/or neurons of the brain triggers increased respiratory efforts and the **blood** becomes **hyperoxygenated** ("bright red").
    - End result is nevertheless a functional tissue anoxia.

Species Susceptibility

- All species are affected: cattle, sheep, and horses most often involved.
- Ruminants are more susceptible than monogastrics to the effects of cyanogenic plants because of the rapidity of ruminal hydrolysis of cyanogenic glycosides which liberates HCN.

Clinical Signs

- Clinical course depends on:
    - Concentration of cyanogenic glycosides in plant.
    - Time period of consumption (rate and duration of consumption).
    - Amount eaten.
    - Previous hydrolysis to free HCN.
- Large amounts may result in death in a few minutes.
- Smaller amounts may be lethal in 20 - 120 minutes. If animals live longer than 120 minutes, they usually recover.
- Initial Signs:
    - Salivation and rapid breathing.
- Progress to:
    - Marked dyspnea, weakness, muscle fasciculations, urination, defecation, rapid heart rate, staggering, mydriasis.
- Terminally:
    - Lateral recumbency, convulsions.
    - Death from respiratory paralysis.

    - The heart may beat for several minutes after respiration ceases.
    - With rapid onset of respiratory paralysis, one may occasionally see cyanotic mucous membranes.

Lesions

- Blood is cherry red and often clots slowly unless the necropsy is delayed.
- Tracheal and pulmonary congestion and/or hemorrhage.
- Ruminal distension; contents smell like "bitter almonds". Note: 20% of the human population are unable to detect this odor.
- Possible gastrointestinal vascular congestion.
- Large exposures may delay carcass decomposition.

Diagnosis

- History of consumption of cyanogenic plants or cyanide salts.
- **Analysis of appropriate specimens for cyanide**:
    - Forage, blood, rumen contents, liver, muscle.
    - Should be placed in air-tight container **immediately** and preferably frozen. May quick-freeze using dry ice.
    - Rather than freezing, an alternative is immersion in 1 - 3% mercuric chloride.
- Field test of forage or other suspected source materials with "picrate paper." (See Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Kendall/Hunt Publishing Company 1984; p. 457. - Available from amazon.com -)
    - In plants, 200 ppm is significant.
- Low concentrations of cyanide in tissues serve as evidence of intoxication.
- Analysis of blood for cyanohemoglobin.
- Differential diagnoses.
    - Nitrate toxicosis.
        - Nitrate poisoning is more common than cyanide toxicosis.
        - Nitrate toxicosis causes chocolate-colored blood.
        - High levels of nitrate may persist in hay; cyanide is usually low in hay.
        - Clinical toxicosis seldom occurs after one feeding.
    - Urea toxicosis.
        - Urea (ammonia) toxicosis may cause rapid deaths and prominent nervous signs.
        - In urea poisoning, there is an ammonia smell to the rumen contents.
        - "Cherry red" blood is seen in toxicoses due to:
            - CN.
            - CO.

Treatment

- Activated charcoal **may** be of significant value, particularly in orally exposed animals.
- Additional goals (urgent) - To split cyanide-cytochrome oxidase bond and cause excretion of cyanide.
- Large animals.
    - One protocol for large animals recommends a mixture of 1 ml of 20% sodium nitrite and of 3 ml of 20% sodium thiosulfate at 4 ml/45 kg BW. Commercial solutions for treatment of prussic acid poisoning are available.
    - Sodium nitrite - large animal dose has also been listed as 10 - 20 mg/kg (as a 20% solution).
        - Intended to induce a measured methemoglobinemia such that the Fe^{+3} in methemoglobin will bind CN^- to reduce the amount available and bound at the Fe^{+3} of cytochrome oxidase. This results in the formation of cyanmethemoglobin.
        - Nitrite may also act as a vasodilator.
    - Sodium thiosulfate 30 - 40 mg/kg (as a 20% solution) is also recommended; and it has recently been suggested that 500 mg/kg is the preferred dose.
        - The enzyme rhodanese causes the sulfur in thiosulfate to react with cyanmethemoglobin to create hydrogen thiocyanate which is excreted in the urine. Thus removing cyanide from the body.
        - Thiosulfate may also be given orally to help detoxify cyanide in the rumen contents.
    - Although methylene blue IV (not for cats) has been suggested by itself at 4 - 6 grams per 454 kg BW, because of slower detoxification of cyanide, this treatment is not recommended.

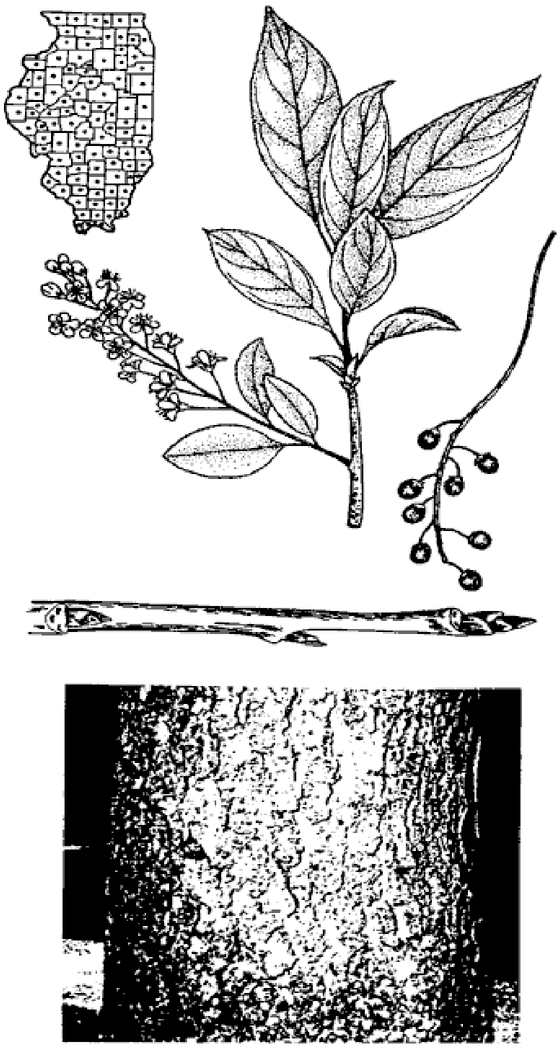
- Small animals.
    - Administer 1.65 ml of a 25% solution of sodium thiosulfate/kg BW and 16 mg of sodium nitrite/kg BW. Repeat dose in 30 minutes if there is no clinical response.
    - Human hospitals may be a source of combined sodium nitrite and sodium thiosulfate (cyanide antidote kits).
    - For cyanide toxicosis associated with smoke inhalation - See Vet Clin North Am, March 1990.

Prevention

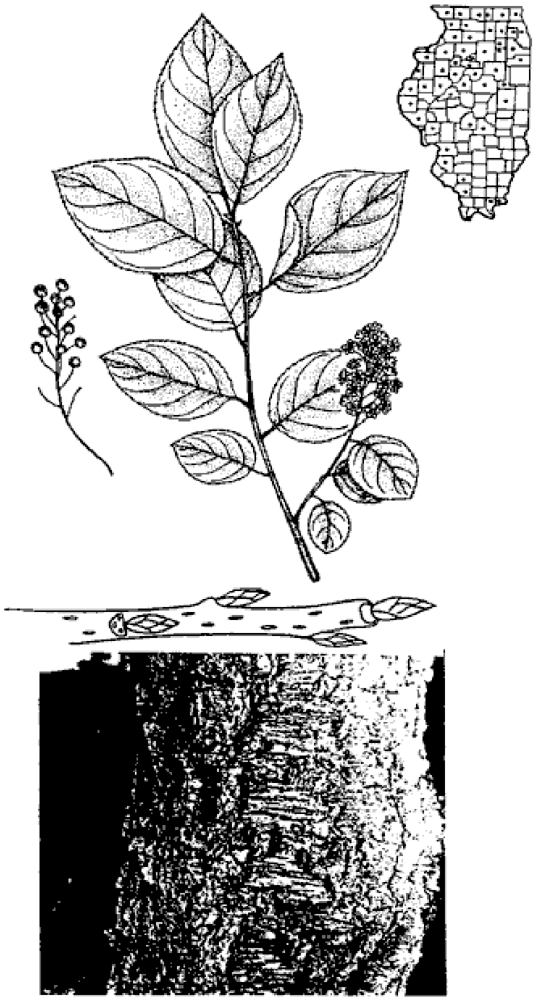
- Prevent exposure.
- Proper forage management.
- Don't graze suspect pastures until plants are 2 feet high.
- If cyanide concentrations in hay or silage were high at cutting, it is sometimes wise to retest before feeding. Given enough time, cyanide tends to dissipate.

Equine "Sorghum - Cystitis - Ataxia Syndrome" (See Toxicants that Cause Paresis or Paralysis)

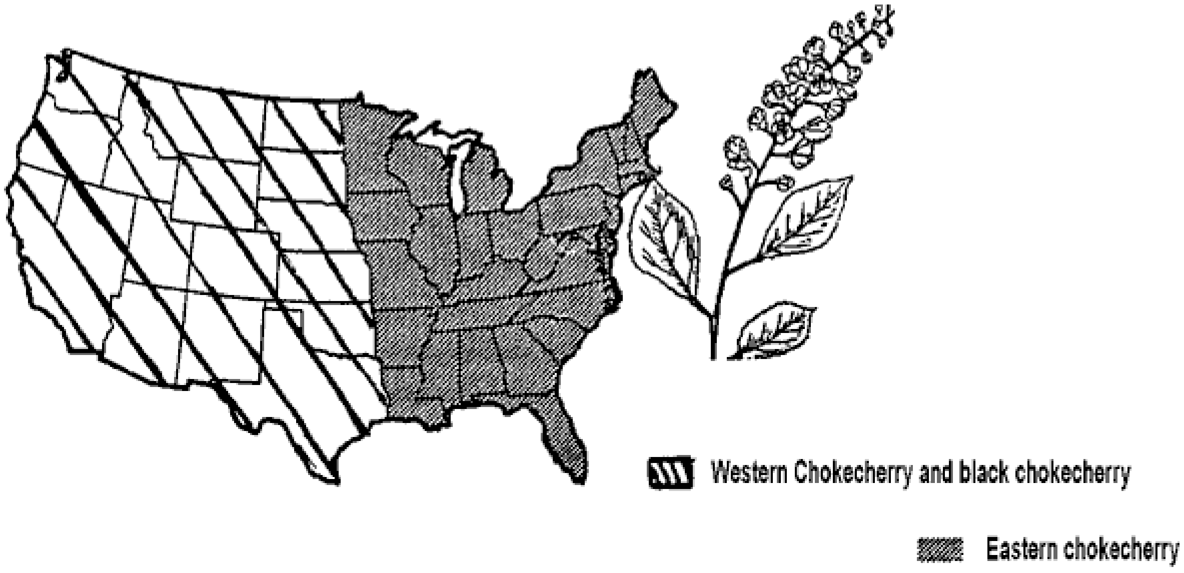
- Lathyrogenic precursors seen in sorghum or sudan may induce.
- May be related to plants metabolism of cyanide or nitrites.
- Clinically: urinary incontinence, cystitis, posterior incoordination.
- Pregnant mares may abort or give birth to foals with arthrogryposis or ankylosis.
- Pathologically - Cystitis and myelomalacia of lower spinal cord.



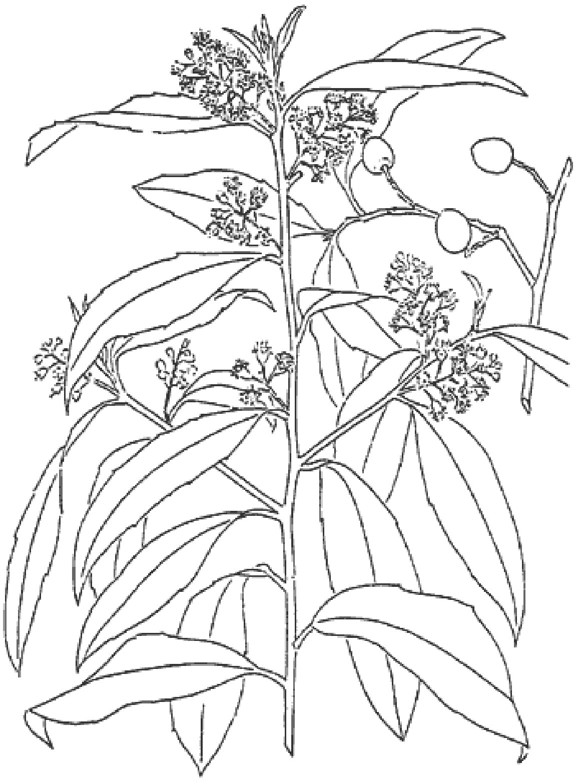
Wild Black Cherry, *Prunus serotina* Ehrh.
Black Cherry, Wild Cherry, Rum Cherry.



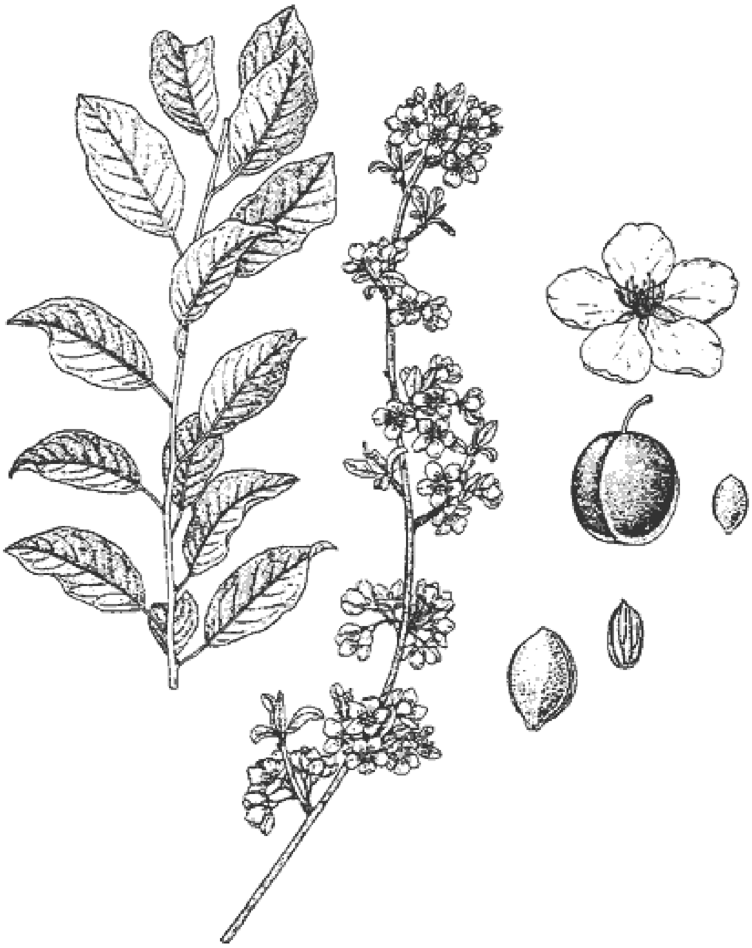
Choke Cherry, *(Prunus Virginiana* L.)



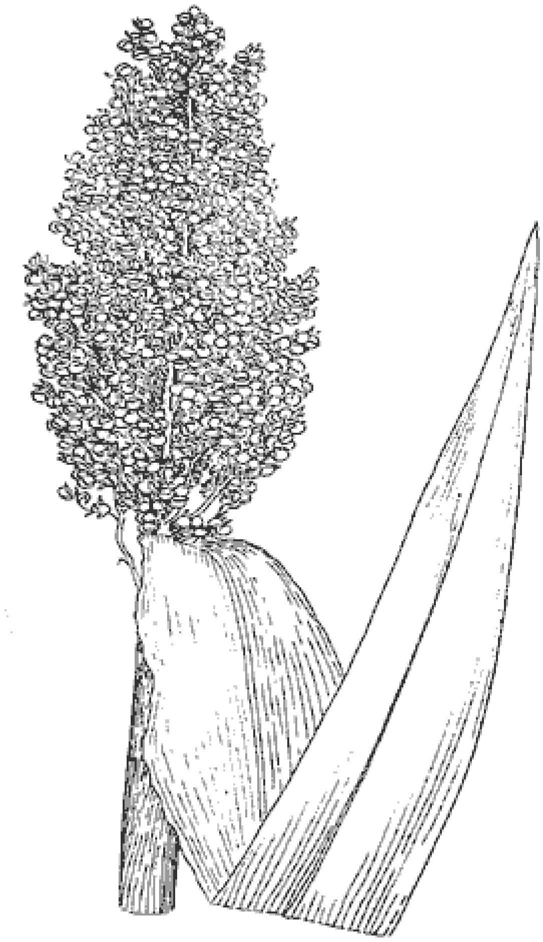
Distribution of Chokecherry



Carolina Laurel-cherry, Cherry-laurel, Mock Orange (*Prunus caroliniana* Ait.)

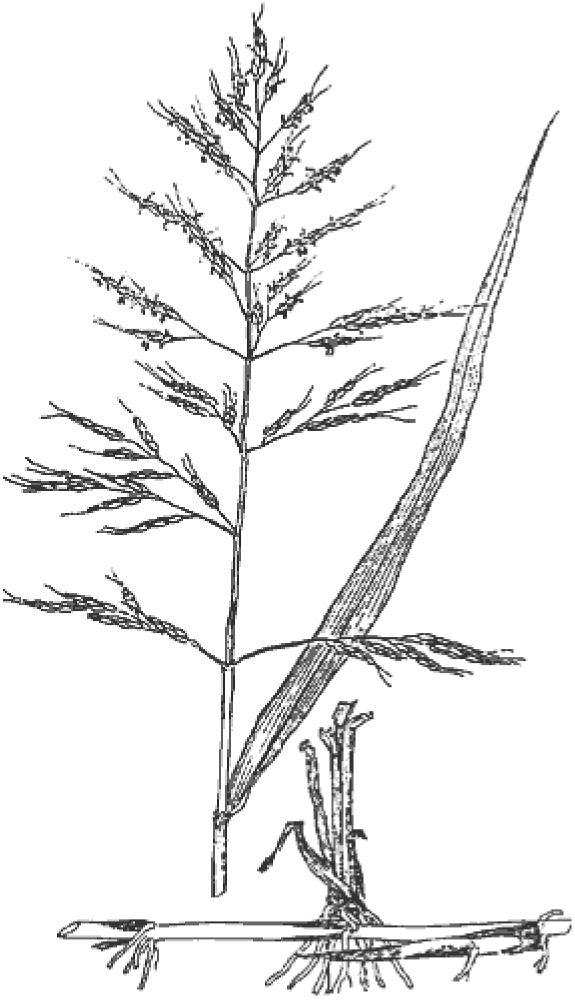


Common Plum - The oval saw-toothed leaves, delicate white flowers (enlarged, upper right), medium sized oval fleshy fruit (right center), and enlarged pit and seed (lower right) are characteristic of this common fruit tree.



Sorghum, Sorgho, Kafir, Dura, Milo, Feterita, Shallu, Kaoliang, Broomcorn, Sudan Grass

Description - Sorghum (*Sorghum vulgare* L.) and its varieties compose a large group of coarse annual grasses, with upright stems 2 to 15 feet in height having 7 to 18 joints. There may be several lateral shoots at the base. The leaves, 1 at each joint, are long, narrow, sharply toothed along the margin, and have a prominent midrib, white, gray or yellow in color. The flower cluster or seed head varies from 5 to 18 inches in length (longer in broomcorn) and may be dense or open and have the branches erect, spreading or drooping, but always in whorls. The seeds and kernels of the various kinds of sorghum vary in size, shape, and especially in color, being white, pink, yellow, buff, brown or reddish brown.



Johnson grass - Flower cluster with leaf; underground rhizome

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Linum spp. - Flax, Linseed

Linum usitatissimum - Flax, Linseed
L. rigidum - Yellow flax
L. lewisii -
L. neomexicanum - Yellow pine-flax

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Inhibit the Function of Cytochromes
All species, esp. herbivores	Minutes to hours	Hours; often lethal	

Family - Linaceae (Flax family)

Description

- Plant - Annual or winter annual, slender, herb about 6 - 10 cm high.
- Stem - Solitary, erect, slender, ridged, glabrous, glaucous, leafy; branched from near base.
- Leaves - Simple, sessile, entire, lanceolate to oblong to linear, acute, 15 - 30 mm long, 2 - 4 mm wide; opposite at bottom; alternate at top; lower leaves shed before fruiting time.
- Flowers - July - October, regular, perfect, 2 - 2.5 cm across; petals, 5, light blue with dark blue lines at base, yellow, persistent, 1 cm long; sepals, 5, glandular, serrate or entire; pistil, compound; calyx, persistent, 7 - 9 mm long.
- Fruit - Capsule, globose, 6 - 10 mm diameter; seeds, narrowly ovate, flattened, 4 - 5mm long, 2 - 2.5 mm wide, brown, smooth, semiglossy.

- Rootstock - Slender taproot.

L. usitatissimum:

- Plant - Slender, erect, annual herb, 3 - 10 cm high (11.8 - 39.4 inches).
- Stem - Solitary, simple, slender, erect, glaborous, leafy, branched near top.
- Leaves: Simple, sessile, entire, alternate, glabrous, lanceolate-linear, 15 - 30 mm (0.6 - 1.2 inches) long, 2 - 4 mm (0.08 - 0.16 inches) wide; lower leaves are sharp pointed; shed before fruit appears.
- Flower - uly to October; 2 - 2.5 cm (0.8 - 1 inch) across; 5 separate, blue or white petals with dark blue lines at the base, 1 cm long; 5 ciliate sepals; 5 stamens; compound pistil; superior ovary; borne in terminal clusters.
- Fruit - Globose capsule about 1 cm (0.4 inch) long; seeds 10, narrowly ovate flattened, brown, smooth, semiglossy, 4 - 5 mm (0.16 - 0.2 inch) long, 2 mm (0.08 inch) wide.
- Rootstock - Slender taproot.

Habitat

- Northwestern USA, Canada, Europe.
- Cultivated for its fiber and oil; linseed cake; screenings.
- *L. usitatissimum* - Also found along roadsides, among other field crops, and in wastelands.
- *L. neomexicanum* - Arizona and New Mexico to Chihuahua, Mexico, range lands, 5000 - 8000 ft elevations.

Toxic Principle

- Cyanogenic glycoside, phaseolunatin (linamarin).
- Linamarase, enzyme in plant material releases HCN.
- May also accumulate nitrite.
- *L. neomexicanum* may contain linotoxin, which, perhaps, is a cyanogenic glycoside, but this is disputed. The toxin is extractable in alcohol.

Toxicity

- Cooked flax is considered edible.
- Flax grown in temperate zones is less toxic than that grown in warmer zones.
- Linseed cake made from immature seed is likely to contain dangerous concentrations of HCN.

Susceptible Species

All classes of livestock.

Signs

The signs are those of cyanide poisoning.

Diagnosis

- Identification of *Linum*, evidence of consumption, and appropriate clinical signs and lesions. Bright red blood.
- Detection of cyanide, in plant material, or frozen rumen contents, blood, liver, or muscle.

Prevention

- Avoid feeding wilted or frosted flax plants.
- Feed linseed cake only in small amounts and without first soaking.

Linum neomexicanum

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Inhibit the Function of Cytochromes
Some spurges (*Euphorbia*) (rare) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Elderberry (leaves and stems) (*Sambucus*) [Cyanogenic glycoside-containing plant] (See Poisonous Plants that Affect the Gastrointestinal Tract)	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Rubberseed meal [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal	
Hydrogen sulfide	(See Toxicants that Primarily Cause Respiratory paralysis)			

- Some Spurges (*Euphorbia*) (Rare) (See Irritating Resins)
- Elderberry (Leaves and stems) (*Sambucus*) (See Plants that Affect the Gastrointestinal Tract)
- Rubberseed meal
- Hydrogen Sulfide (See Toxicants that Primarily Cause Respiratory Paralysis)

Section XVIII: Toxicants that Decrease the Ability of Hemoglobin to Carry Oxygen

Carbon Monoxide

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Smoke Inhalation

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Carbon Monoxide
All species	Minutes to hours	Hours to 2 days, often lethal	

Potential Pathophysiologic Processes

- The primary cause of death in most smoke inhalation toxicoses in small animals is believed to be carbon monoxide (CO) toxicosis.
- Thermal injury to the respiratory tract is another part of the syndrome in many cases.
- Toxic injury to the respiratory tract from noxious gases and particulates is often a third significant component of the process.

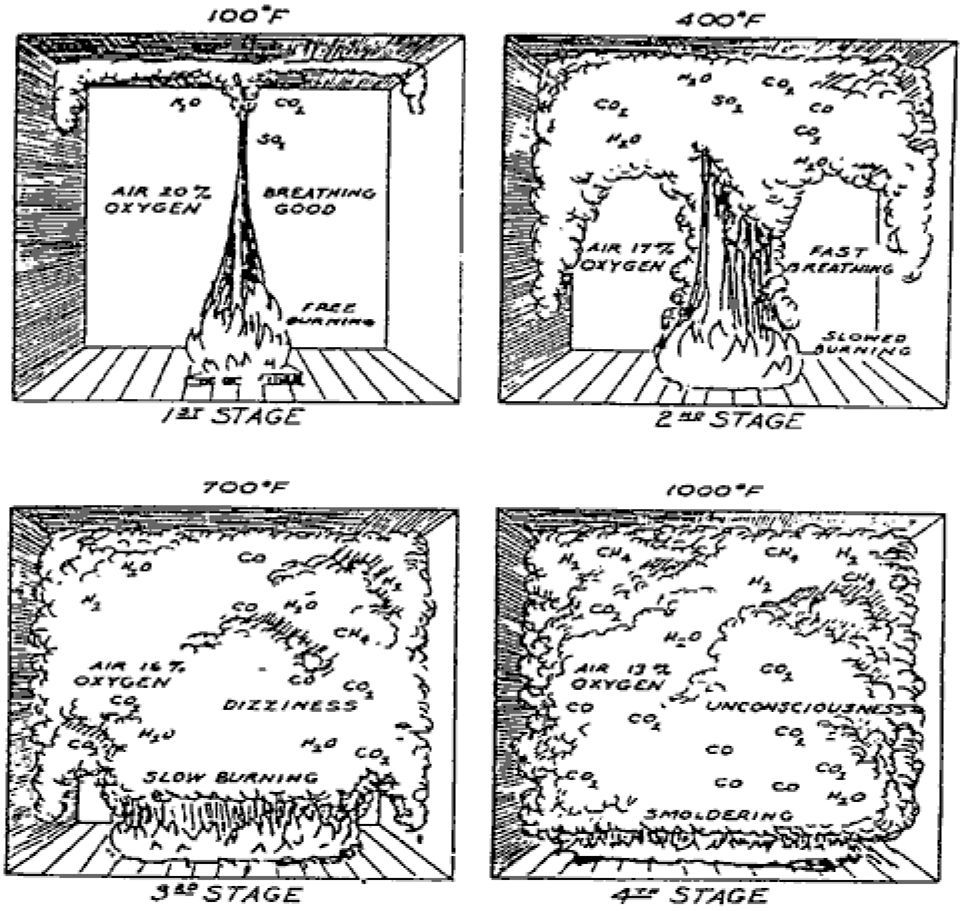

Figure 1. Progression of fire in a closed room.

Amount of Oxygen Released from the Hemoglobin in the Tissues of the Normal Animal

Note below that the total quantity of oxygen bound with hemoglobin in the normal arterial blood (PO_2 of 95 mmHg) is approximately 19.4 ml. On passing through the tissue capillaries, this amount is reduced to 14.4 ml (PO_2 of 40 mmHg), or a total loss of about 5 ml of oxygen from each 100 ml of blood. Then, when the blood returns to the lungs, the same quantity of oxygen diffuses from the alveoli to the hemoglobin, and this too is carried to the tissues. Thus, under normal conditions, about 5 ml of oxygen is transported by each 100 ml of blood during each cycle through the tissues.

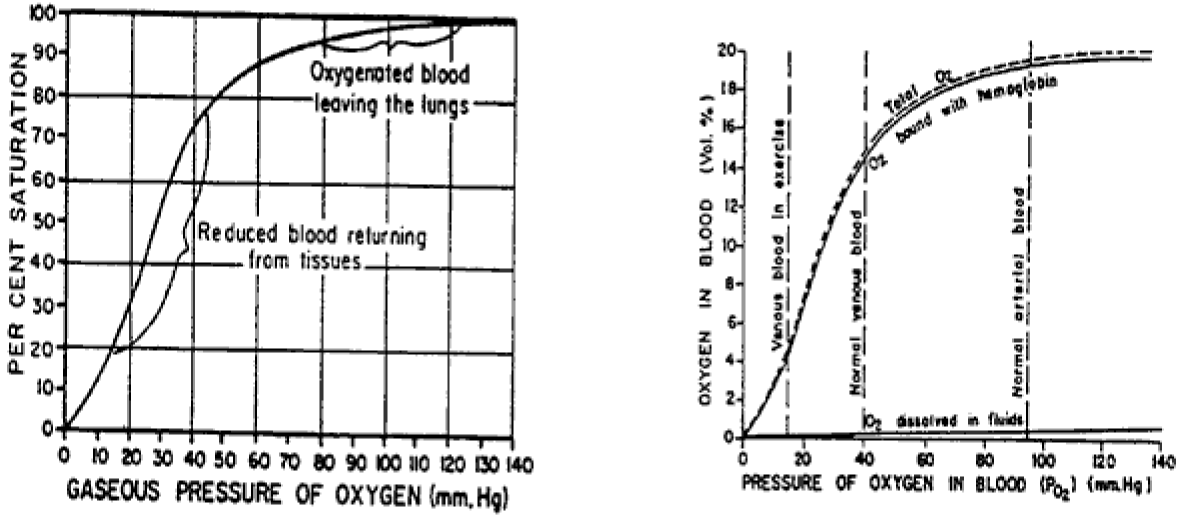

Figure 2. Oxygen-hemoglobin, oxygen-water (of the blood), oxygen-blood dissociation curves; quantity of oxygen in each 100 ml of normal blood **a**) bound with hemoglobin; **b**) dissolved in the water of the blood; and **c**) total oxygen in both forms.

The Utilization Coefficient: Oxygen Utilization in Normal Animals

The fraction of the hemoglobin that releases oxygen as it passes through the tissue capillaries is called the utilization coefficient. Normally, this is approximately 27% of the hemoglobin, or in round figures, the normal utilization coefficient is approximately one-fourth. During strenuous exercise, however, up to a maximum of 77% of the hemoglobin can give up its oxygen, or in round figures, the utilization coefficient is then approximately three-quarters. Nevertheless, in local tissue areas where the blood flow is very slow or the metabolic rate very high, utilization coefficients approaching 100% have been recorded - that is, essentially all the oxygen is removed.

Pathophysiology of Smoke Inhalation

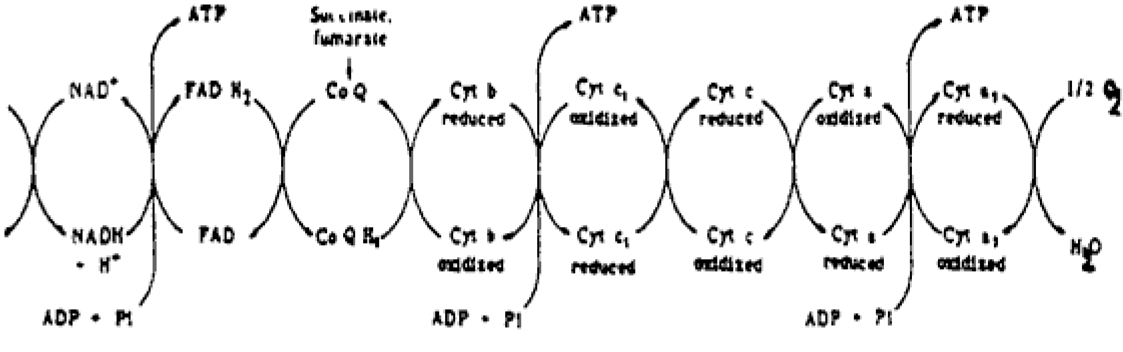

Figure 3. Outline of respiratory chain oxidation. Pi, inorganic phosphate; FAD, flavoprotein; CO Q, coenzyme Q; R, proton donor; Cyt, cytochrome. Failure of oxygen delivery causes cessation of function of the cytochromes: the major source of energy (from food, etc.) conservation (in the form of ATP) in the body. Different aspects of smoke inhalation can cause a functional "asphyxia" at the tissue level by virtue of:

a) reduced oxygen delivery by the blood, **b**) reduced exchange of gases in the lung, and/or **c**) direct blockade of cytochrome oxidase (cyanide).

A. Carbon Monoxide Toxicosis

- Produced by incomplete combustion: therefore produced by fires in closed spaces (areas with limited oxygen)
- Colorless, odorless, tasteless, and non-irritating.
- Does not injury the lung but decreases the oxygen-carrying ability of blood as a result of its binding to hemoglobin.
- CO also **shifts the oxygen-hemoglobin dissociation curve to the left, which impairs oxygen unloading** (by the adjacent hemoglobin molecules not bound to CO) at the tissue level. This is a **major cause of tissue hypoxia** in CO poisoning.
    - Explanation - Hemoglobin has 4 subunits, each of which contains one heme moiety attached to a polypeptide chain. Heme is a porphyrin and one atom of ferrous (Fe++ iron). Thus, there are four sites on hemoglobin that bind one oxygen molecule (O_2) each. The hemoglobin molecule changes slightly with each oxygen atom released or taken up. This changes the affinity for the remaining oxygen atoms - and this gives rise to the oxygen dissociation curve (the plot of the relationship between percent oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood). Because CO induces a shift of the oxygen dissociation curve to the left, the blood retains a higher percentage of the oxygen than normal in the tissues (higher percent saturation of hemoglobin despite lower partial pressure of oxygen in the blood). Therefore, less oxygen is delivered (released) to the tissues than normal. **Note** - That alkalinization of the animal, low body temperatures, and methemoglobinemia also shift the oxygen dissociation curve to the left and are generally contraindicated with significant CO on board.
- **Note -** The fire also consumes oxygen, therefore there is less oxygen to compete for hemoglobin than would normally be the case. However, animals with CO toxicosis generally do **not** have tachypnea/hyperpnea because PO_2 levels are not low enough to trigger that sort of response. Animals may be comatose, and may develop a degree of brain (or heart) damage if the condition is sufficiently severe. The blood (antemortem or at necropsy) and muscles (at necropsy) will be bright red.
- Cardiac output is decreased - The cause **may be** CO induced cerebral hypoxia and a secondary increase in pulmonary vascular resistance.
- Result - Tissue hypoxia, hypercapnia.
- Tissue hypoxia results in lactic acidosis.
- 10% or less COHb - No clinical signs.
- 10% to 20% COHb - Shortness of breath on moderate exercise, mild dyspnea.
- 30% COHb - Increased irritability of the animal, ataxia, nausea, vomiting.
- Over 40% COHb - Confusion, collapse, possible coma.
- 50% to 60% CoHb - Respiratory failure and death may occur; possible convulsions, which are most likely to be agonal in nature.
- Half-life of CO in the body: is approximately 4 hours (in all likelihood, this is based on an assumption of normal respiratory exchange - i.e., no significant damage to the lung) (See Treatmentsection below).
- **Combination of hemoglobin with carbon monoxide**.
    - Carbon monoxide combines with hemoglobin at the same point on the hemoglobin molecule as does oxygen. Furthermore, it binds with approximately 210 - 240 times as much tenacity as oxygen, which is illustrated by the carbon monoxide-hemoglobin dissociation curve below.

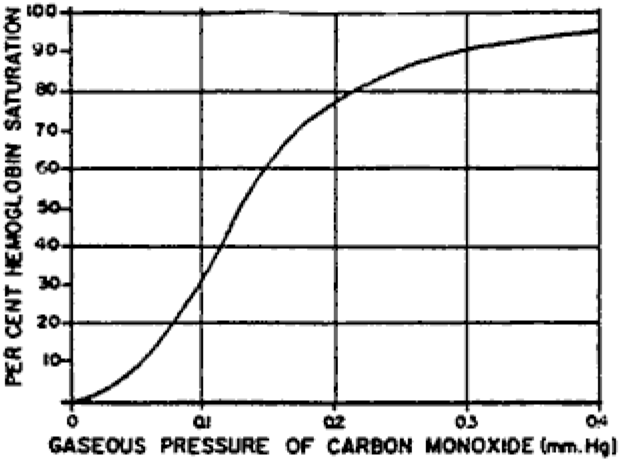

Figure 4. The carbon monoxide-hemoglobin dissociation curve.

- This curve is almost identical with the oxygen-hemoglobin dissociation curve except that the pressures of the carbon monoxide are at a level 210 times less than those in the oxygen-hemoglobin dissociation curve shown previously. Therefore, a carbon monoxide pressure of only 0.5 mmHg in the alveoli, 210 times less than that of the alveolar oxygen, allows the carbon monoxide to compete equally with the oxygen for combination with the hemoglobin and causes half the hemoglobin in the blood to become bound with carbon monoxide instead of with oxygen. A carbon monoxide pressure of 0.7 mmHg (a concentration of about 0.1 percent) is lethal.
- A patient severely poisoned with carbon monoxide can benefit from administration of pure oxygen, for oxygen at high alveolar pressures removes carbon monoxide from its combination with hemoglobin far more rapidly than can be achieved at the low pressure of atmospheric oxygen. That is, the pressure allows the oxygen actually to force its way into the hemoglobin molecule and thereby to displace the carbon monoxide.
- The patient can also benefit from simultaneous administration of a few percent carbon dioxide because this strongly stimulates the respiratory center. The resulting increase in alveolar ventilation reduces alveolar carbon monoxide concentration and thereby increases the release of carbon monoxide from the blood.

Table 1. Signs or Symptoms of Reduced Levels of Oxygen Due to Fire Conditions

Percent of Oxygen in Air	Signs or Symptom (Human)
20 (or above)	Normal
12 to 15	Muscular coordination for skilled movements lost
10 to 14	Consciousness continues but judgment is faulty and muscular effort leads to rapid fatigue
6 to 8	Collapse occurs quickly but rapid treatment would prevent fatal outcome
6 (or below)	Death in 6 to 8 minutes

From Underwriters Laboratories, Inc., *Bulletin of Research*, No. 53, July 1963, p. 49. Information abstracted from *National Fire Protection Association Quarterly*, "Fire Gas Research Report", Vol. 45, No. 3:280-306 (1952).

Table 2. Signs and Symptoms at Various Concentrations of Carboxyhemoglobin

% COHb	Signs and Symptoms (Human)
0 to 10	No signs or symptoms
10 to 20	Tightness across forehead,

	possible slight headache dilation of the cutaneous blood vessels
20 to 30	Headache and throbbing in the temples
30 to 40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting, and collapse
40 to 50	Same as above, greater possibility of collapse, syncope, and increased pulse respiratory rates
50 to 60	Syncope, increased respiratory and pulse rates, coma, intermittent convulsions, and Cheyne-Stokes respiration
60 to 70	Coma, intermittent convulsions, depressed heart action and respiration leading to death within hours
70 to 80	Weak pulse, slow respiration leading to death within hours
80 to 90	Death in less than an hour
90+	Death in a few minutes
From: Schulte, J. H., *Arch. Environ. Health*, 2:524 (1963).	

Table 3. Time to Physical Incapacitation (TI) And Time to Death (TD) in CO, HCN, And CO + HCN Atmospheres

	HCN - 450 PPM	**CO - 13,500 PPM**	**CO + HCN**
Rotary Cages			
TI Minutes	4.1 ± 0.7	2.4 ± 0.3	2.0 ± 0.3
TD Minutes	10.9 ± 2.0	5.8 ± 1.2	3.7 ± 0.4
Insert Cages			
TD Minutes	7.9 ± 2.0	6.3 ± 1.5	3.2 ± 0.4

B. Excessive Heat

- May directly injure upper respiratory mucosae: full expression of effects is often delayed.
- May result in laryngospasm, erosions, edema: possibly life-threatening.
- Mucosal burns of mouth, nasopharynx, pharynx, or larynx may lead to upper airway obstruction at any time during the first 24 hours after the burn.
- True thermal damage to the lower respiratory tract is rare unless live steam or explosive gases are inhaled.
- Airway damage may occur, however, from inhalation of **superheated soot** and **other particles** resulting from incomplete combustion.
- Ocular irritation or injury may also be present.

C. Noxious Gases and Particulates

- Full expression of effects are often delayed depending on the types of gases and/or particulates that are generated by the fire and the amounts involved.
- Gases may be carried in with superheated particulate matter.
- Toxic products may include short-chain **aldehydes**, **acids** (and oxides of sulfur and nitrogen which are converted to acids in the respiratory tract), and **ketones** from burning furniture, fabrics, plastics, etc. Wood smoke has 20 to 25 times the aldehydes present in smoke from burning kerosene and the former is much **more** lethal. **Benzene** or **cyanide** may be produced by some burning processes. One source of **cyanides** is burning urethanes. Benzene may act as a local anesthetic to permit deeper entry into the lung of acids and other noxious gases.

- **Carbon dioxide**, also produced during burning is a **simple asphyxiant** which further aggravates the lack of oxygen available to the cells.
- As lung damage is manifested during the first days following smoke inhalation, ventilation/perfusion abnormalities may occur possibly including **intrapulmonary shunting**. Compensatory tachypnea is likely in seriously affected animals.
- Pulmonary **macrophages are also poisoned** by smoke, which severely impairs macrophage function, which enhances the likelihood of delayed bacterial pneumonia.

Clinical Signs and Effects

- **Stage I** (during smoke inhalation).
    - Initial hyperventilation, hypoxia, hypercapnia, acidosis.
    - Decreased cardiac output, bronchospasm.
    - Carbon monoxide poisoning.
    - After several minutes, apnea may occur (this may be an effect of factors other than or in combination with carbon monoxide rather than due to CO alone).
    - Three possible outcomes when carbon monoxide alone is involved: recovery with no permanent effects, recovery with CNS damage (the brain is generally regarded as the most sensitive tissue), death.
- **Stage II** (0 to 30 minutes after removal from smoke)
    - Hypercapnia, mild hypoxia.
    - Severely depressed cardiac output.
    - Increased vascular resistance.
    - Hyperventilation.
    - Carboxyhemoglobinemia.
- **Stage III** (2 to 24 hours after removal from smoke)
    - Increasing hypoxia.
    - Decreasing pulmonary compliance.
    - Altered ventilation:perfusion rations.
    - Clearing of CO.
    - Mildly depressed to normal cardiac output.
    - Pulmonary edema.
- **Stage IV** (after 24 hours)
    - If bacterial pneumonia develops, lung failure is common.
    - In the absence of bacterial pneumonia, recovery is common (do not make a prognosis too soon - i.e., hesitate for a few days at least).

Smoke Inhalation - Emergency Workup (quick list; see below for details).

- Obtain arterial blood gases on room air if possible.
- Examine skin to evaluate burns, especially facial.
- Carefully examine mucosal surfaces for burns/soot.
- Perform a thorough neurologic, corneal, and funduscopic examination.
- Auscult over the upper airways and thorax.
- Examine the saliva for carbonaceous particles.
- Perform an EKG for older or more significantly affected animals.
- Utilize laryngoscopy or bronchoscopy if available for animals with significant facial burns, soot in pharynx, carbonaceous particles in saliva, dyspnea, or upper airway effects.
- Obtain baseline thoracic X-rays.

Diagnosis and Monitoring (details)

- Monitor for acrid smell of smoke on the haircoat.
- Ask rescuers whether the animal was able to move away from the fire on its own or not.
- Carefully examine the external animal and oral-pharyngeal area; check for laryngospasm immediately.
- Auscult thoroughly.
- Examine carefully for hoarseness, expiratory wheeze, or carbonaceous sputum which indicate serious involvement.
- Determine carboxyhemoglobin concentrations (as percent saturation of hemoglobin in the carboxyhemoglobin state) and blood gases on whole blood.

  - Venous blood samples are generally evaluated for carboxyhemoglobin and arterial samples are tested for the common blood gases pO_2, pCO_2, pH.
  - Serial carboxyhemoglobin determinations on blood are of value in monitoring respiratory function as are ordinary blood gases. When carboxyhemoglobin concentrations are comparatively high, initial assessment of paO_2 may be misleading, since the oxygen carrying capacity of the hemoglobin is reduced. The **arterial partial pressure of oxygen (paO_2) can still be normal (as will the calculated value for oxygen saturation derived therefrom) even in moderately severe CO toxicosis**. Thus, the paO_2 can be normal, although the **O_2 content is actually dangerously low**. It is, therefore, helpful to **measure the oxygen saturation** of the blood directly **using a hemoximeter**.
- Evaluate color of blood to see if it is cherry red from CO, or less often from cyanide (usually die fast from cyanide); red color can mask actual tissue hypoxia and poor perfusion from shock.
- Utilize radiographic evaluation: often normal for first 16 to 24 hours after a moderate to severe injury; therefore can use for comparison to subsequent radiographs. Radiographs help to reveal atelectasis, edema, hemorrhage, infection. Most often see bronchial or peribronchial densities or interstitial infiltration, indicative of edema. The presence of air bronchograms may be seen in instances of edema or pneumonia.
- A transtracheal aspiration biopsy may be used to assess the relative numbers of necrotic and normal cells and the presence of particulate debris.
- Bronchoscopy requires general anesthesia for 10 to 15 minutes and must, therefore, be used only when the risks are not excessive and always with caution. Can be used to assess airway changes including mucosal erythema, hemorrhage, ulceration, edema, and carbonaceous particles.

Treatment

- Removal from the toxic environment.
- Face mask administration of oxygen at the site of the fire is very helpful in human medicine and the same would apply in veterinary medicine if possible.
- Be certain there is an adequate airway: may involve oropharyngeal suction, removal of debris, and maintenance of an unobstructed flow of air.
- With significant laryngospasm, it may be necessary to utilize endotracheal or tracheostomy intubation (don't wait until the last minute to try to intubate!); may be followed by positive pressure ventilation.
- For CO poisoning, use 100% oxygen therapy or, if available, O_2 with a few percent CO_2. The 4-hour half-life of CO in the blood when exchanged for oxygen in room air can be decreased to 30 to 40 minutes when 100% O_2 is breathed. Also, breathing 100% O_2 can result in enhanced delivery of oxygen to the tissues, since dissolved oxygen in the blood can enter the tissues even before CO is significantly displaced from hemoglobin.
- Oxygen is preferably provided in an oxygen cage, although masks may be used; it may be necessary to sedate the seriously hypoxic but difficult to manage patient and then to deliver the oxygen after intubation. Usually 8 to 12 breaths per minute are used for approximately 30 to 40 minutes.
- Positive-pressure ventilation is also of value for pulmonary edema if it is involved.
- Intravenous fluids are used in shock states to help maintain cardiac output and thereby enhance oxygen delivery to the tissues. Lactated Ringer's has been suggested as the fluid of choice. Fluid administration must be **carefully monitored to avoid overhydration to avoid potentiating pulmonary edema**.
- Corticosteroids are **not recommended** since patients with both smoke and thermal injury have experienced reduced survival rates when these drugs were used. Corticosteroids are used only for animals with serious circulatory shock.
- Antibiotics given prophylactically are **not recommended** although, in instances in which infection is developing, antibiotics are indicated and are generally selected on the basis of airway culture and sensitivity test. Most infections are with gram-negative organisms which should influence initial therapy while awaiting culture results.
- Bronchodilator therapy is used to alleviate reflex bronchospasms (use when patient exhibits wheezing); aminophylline (6 to 10 mg/kg IM, IV, or orally, TID) or theophylline elixir (0.4 ml/kg orally TID), or terbutaline sulfate (Brethine; 5 to 10 mg/kg orally TID may be used.
- Surface burns and the use of tracheostomy tubes increase the likelihood of secondary infections and decrease the likelihood of survival. Proper handling and use of tracheostomy tubes is essential in controlling the incidence of bronchopneumonia.
- Cats or dogs with cyanide toxicosis should be handled with care. Cats and, to a lesser degree, dogs are more susceptible than humans and large animals to agents that oxidize hemoglobin to methemoglobin (such as nitrite), so that protocols (such as nitrite + sodium thiosulfate) for humans and large animals with cyanide toxicosis may be unsafe for small animals, especially the cat.

Note - See also Vet Clin North Am, March 1990.

Methylene Chloride

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Carbon Monoxide
(See Toxicants that Cause CNS Depression)			

Synonyms - Dichloromethane, methylene dichloride, methylene bichloride

Sources

- Paint and varnish strippers
- Wood stains
- Solvent/degreasers
- Toxic exposures can result from inhalation, ingestion, or skin or ocular contact.
- **Note** - Combustion of methylene chloride can produce highly toxic phosgene gas, which may damage the lungs.

Metabolism

- A portion of methylene chloride is converted to carbon monoxide. At least in neonatal puppies (and probably many other species and all life stages with sufficient exposure), persistent exposure may lead to clinical carbon monoxide toxicosis.
- Mouse liver produces formaldehyde (a mutagen) from methylene chloride and mice develop DNA-protein cross links as well as liver and lung tumors following exposure to methylene chloride.
- Hamster liver did not develop DNA protein cross links following exposure to methylene chloride and hamsters did not develop liver or lung lesions as in mice.
- Rats are also resistant to methylene chloride-induced liver tumors.
- There is no epidemiologic evidence to indicate the methylene chloride is carcinogenic in human beings. Mouse, primary hepatocytes produced DNA-protein cross links, but human hepatocytes did not, following exposure to methylene chloride.

Clinical Signs

- Ataxia, incoordination, stupor or increased irritability.
- Nausea.
- Pulmonary edema.
- As with carbon monoxide toxicosis, animals may exhibit carboxyhemoglobin, and associated bright red blood, as well as red muscle tissues.

Diagnosis

- Identification of methylene chloride in source materials, digestive tract contents, and tissues.
- Elevated carboxyhemoglobin, which is more persistent after cessation of exposure than with carbon monoxide gas. This is because of continued metabolism of absorbed methylene chloride.

Treatment

- Prevent absorption: remove animals from in enclosed spaces in cases of inhalation or dermal exposure. Bathe with detergent to remove from skin.
- Increase oxygen available to animals with carbon monoxide toxicosis.
- Ingestion of significant amounts may be unlikely due to irritant effects on the digestive tract mucosae.
- Apparently, there are no data on the use of emetics, lavage, cathartics, and activated charcoal. However, if there are no apparent contraindications and ingestion of large amounts has recently occurred such treatments are warranted.

Introduction to the Toxicology of the Erythrocytes, Platelets, and Clotting Proteins

1. Development and Functions of the Red Blood Cells (RBCs)

- Major function is to serve as a small, flexible container for hemoglobin that serves to deliver oxygen from the lungs to the tissues.
- Nucleated RBCs in fish, amphibians, reptiles, and birds.
- Non-nucleated RBCs in mammals.
- Hemoglobin contains iron (Fe^{++}) and has a relatively high affinity for O_2.
    - Blood with a low oxygen concentration takes on O_2 in the lungs and, because of competition for binding with 2,3-diphosphoglycerate (2,3-DPG) and protons (H^+), oxygen is released from hemoglobin in the tissues.
        - Metabolism in the tissues and buffering of the blood (by the kidneys and lungs) creates a gradient such that the tissues are acidic relative to the blood. Thus, at the level of the capillaries, hemoglobin releases its oxygen, which is then used by the tissues especially for oxidative phosphorylation.
- Hematopoiesis = production of blood cells.
    - Fetal and Neonatal Hematopoiesis and Fetal Blood
        - Initially hematopoiesis occurs in the yolk sac. Even in the human fetus, these are nucleated RBCs, and they contain an embryonal form of hemoglobin.
        - The liver, the spleen, and eventually the bone marrow later become sites for production of RBCs. The RBCs produced in the liver are not nucleated.
        - At birth, only the bone marrow is producing RBCs (in human beings). Still, even after birth, the liver and spleen can become sites of extramedullary hematopoiesis.
        - Human beings *in utero* produce fetal hemoglobin. There is a gradual transition from production of fetal to adult hemoglobin after birth so that by 6 months old babies are producing 100% adult hemoglobin.
        - Fetal hemoglobin binds 2,3-DPG less avidly than does adult hemoglobin so that the fetus can extract O_2 from the maternal circulation.
        - In several species of domestic animals, fetal and adult hemoglobins are identical. The strategy in these species is simply to have less 2,3-DPG in the blood of the fetus than of the adult.
        - Erythropoietin stimulates the production of RBCs. Unlike in the adult, in the fetus, erythropoietin is produced by the liver.
- Hematopoiesis and Blood from 6 Months of Age to Adulthood (Human)
    - Bone marrow contains multipotential stem cells that can become RBCs, megakaryocytes (precursors to platelets), or leukocytes (white blood cells = WBCs).
        - Abnormally low numbers of these elements in the blood are termed anemia, thrombocytopenia, and leukopenia, respectively.
    - Erythropoietin
        - In the adult, erythropoietin is produced by the kidney.
        - Erythropoietin causes the multipotential stem cell to become a proerythroblast, thereby committing it to a sequence of steps resulting in its becoming a RBC.
- At the end of their lifespan, RBCs are normally removed and destroyed by the spleen. Some of the nutrients are recycled in the body, some leave via the liver and/or kidney. Removal of the spleen does not necessarily prolong the life of the RBCs, because the other parts of the reticuloendothelial system (esp. the liver and the bone marrow) take over this role of the spleen. The RBCs must pass through fine channels lined with macrophages in the spleen, and if they are deformed (e.g. if they are old cells without the energy to maintain their normal configuration, as a result of Heinz bodies, or if they are parasitized cells, they are very likely to be recognized as abnormal, engulfed, and destroyed.
- Hemoglobin normally binds to four O_2 molecules, and releases three of them in a step-wise fashion in response to a low oxygen concentration and high acidity (low pH).
- Hemoglobin in RBCs transports O_2 to the cells, and on the return trip, CO_2 is carried in the RBCs in one of three forms: in the form of bicarbonate (large amount) after conversion by the enzyme, carbonic anhydrase; in simple solution (small amount); and after attaching to free amino groups of hemoglobin to form carbaminohemoglobin (R-NH-COOH) (small amount).
- Hemoglobin is the main acceptor of hydrogen ions (H^+) in the blood, accounting for about 85% of the buffering capacity of the blood.

2. Development and Functions of the Platelets

- The liver is the initial site of the production of platelets in the developing fetus.
- The bone marrow becomes the most important site of production thereafter.
- Platelets are the first line of defense against hemorrhage - form a "patch" over the break in a blood vessel & they help trigger the clotting cascade.
- Normally, platelets are non-sticky, but when exposed to connective tissue collagen (as a result of a break in a blood vessel), they react to release their granules and become extremely sticky, aggregate, and form a "platelet plug".
- Platelets become sticky (and small blood vessels constrict under the influence of the platelet-derived prostaglandin, thromboxane A_2.
- Unlike the other non-steroidal anti-inflammatory drugs, aspirin, even at low doses, irreversibly acetylates the enzyme cyclo-oxygenase, which is the first step in the production of the prostaglandins. Thus, for the life of the platelet, its production of thromboxane is prevented. For this reason, aspirin is a useful drug to help prevent unwanted clotting that can contribute to "vascular accidents".

Production and Function of the Clotting Proteins

- The liver is the site of the production of the clotting proteins.
- Proteins are involved in two cascades: the intrinsic and the extrinsic pathway.
- These produce insoluble fibrin that reinforces the platelet plug. Eventually fibroblasts may infiltrate the area occupied by fibrin resulting in scar formation.
- A final carboxylation reaction catalyzed by vitamin-K_1 serves as the activation step in the production of some of the key clotting proteins in the blood [e.g. factors II (= prothrombin), VII, IX, and X].
- Vitamin-K_1 in its active hydroquinone form is essential in this process. As it functions, it is converted to its epoxide, rendering it inactive until it can be reconverted to the active form by the enzyme vitamin-K epoxide reductase.
    - Drugs used to prevent clotting, such as warfarin, natural toxins, such as dicoumarol, and rodenticides, such as brodifacoum, diphacinone, and bromadiolone inhibit vitamin-K epoxide reductase, thereby preventing the normal recycling of vitamin K to its active form and thus inhibiting the production of the active forms of the clotting proteins.
        - Compounds that inhibit vitamin-K epoxide reductase, prevent the normal frequent recycling of the vitamin from its used (inactive) epoxide form, to its active hydroquinone form.
    - Warfarin is highly protein bound in the plasma; therefore, when given with other drugs that are as tightly (or more tightly) bound, such as some sulfonamides or phenylbutazone, warfarin becomes displaced from the albumin, thereby increasing the dose that reaches the liver. This may result in marked inhibition of production of clotting proteins. This is the reason why people and animals on warfarin therapy are so prone to drug interactions that lead to severe hemorrhage.

4. Agents that Damage the Bone Marrow Stem Cells and thus Result in Depletion of All Three Series of Formed Elements (RBCs, platelets, WBCs).

- A marked deficiency of all three is termed pancytopenia.
- Pancytopenia can result from high level exposure to:
    - Radiation.
    - Benzene.
        - Metabolically activated (site unclear - liver or bone marrow?) to a cytotoxic compound, possibly benzoquinone, that is cytotoxic to the bone marrow cells.
    - Anti-cancer drugs.
    - Lindane (an organochlorine insecticide).
    - Chlordane (another organochlorine insecticide).
    - Nitrogen mustards.
    - Arsenic (rare effect).
    - Chloramphenicol (antibiotic; humans uniquely sensitive); most other species effects are more reversible.

        At least in some cases, seems to be mediated by an immunologic mechanism.

    - Trinitrotoluene (TNT; explosive).

    - Gold salts (used as anti-rheumatic drugs).
    - Hydantoin derivatives.
    - Phenylbutazone.
- With the above agents, sometimes one series or another may be more sensitive so that, depending on the toxicant and the dose, the problem may appear to be more of an anemia, a thrombocytopenic disorder, or a leukopenia.
- Platelet deficiency can also result from autoimmune disorders, some of which can be induced by chemicals, e.g.:
    - Quinidine (used to correct cardiac arrhythmias).
    - Phenacetin (an obsolete non-steroidal anti-inflammatory drug).

5. Toxicoses that are Associated with Damage to RBCs or Hemoglobin, or that, via Other Mechanisms, Cause Hemoglobin to Fail to Serve as an Effective Carrier of Oxygen.

Agents that Interfere with Blood Production:

- Severe damage to bone marrow such that RBCs are not being produced is termed aplastic anemia.
- Lead: inhibits several enzymes involved in production of hemoglobin.
    - Inhibits heme synthetase = the enzyme responsible for insertion of the iron atom into the protoporphyrin molecule, thus creating heme. Without heme, the hemoglobin is an ineffective carrier of oxygen. Also, the person will tend to release immature RBCs into the blood. Increased numbers of RBCs with basophilic stippling and increased numbers of nucleated RBCs are seen in the blood.
    - Inhibits d-aminolevulenic acid dehydratase.

Agents that dissolve RBC cell membranes:

Saponins (from plants; although this effect is rarely seen); detergent-like compounds that dissolve membranes (cause digestive tract damage and upset and when absorbed in sufficient amounts cause hemolysis.

Agents that Causes Hemolysis - Causation not Fully Worked Out:

- Heinz bodies involved (generally related to oxidative injury).
    - Arsine (arsenic hydride) - Gas produced by charging batteries (Heinz bodies involved).
    - Stibine (antimony hydride) - Gas (Heinz bodies involved) (antimony is very toxicologically similar to arsenic in other ways as well).
    - Phenols - esp. concentrated phenol, cresol.

        Some old forms of Lysol ® contained 0.1% of *O*-phenylphenol; however, it also contained 79% ethanol posing an additional toxicologic risk.

    - Propylene glycol (e.g., when given i.v.; generally not with ingestion of Sierra ® antifreeze).
    - Ascorbic acid (vitamin C).
    - Ingestion of crude oil by marine birds.
    - Phenylhydrazine (intermediate in chemical industry).

Agents that Cause Oxidative Injury to RBCs (may overlap with previous section):

- Effects include: formation of Heinz bodies, hemolysis, and production of methemoglobinemia.
- Heinz bodies = masses of denatured hemoglobin that precipitate and become covalently bound to the interior surface of the plasma membrane of the erythrocyte. These result in recognition by the spleen as a potentially "sick" erythrocyte; spleen ruptures the RBCs thereby releasing the hemoglobin and resulting in hemolytic anemia. This type of hemolytic anemia is termed a Heinz body anemia.
- Methemoglobin: Oxidation of the ferrous iron (Fe^{++}) in hemoglobin to ferric ion (Fe^{+++}) creates methemoglobinemia, thereby changes the molecule from highly efficient, to a very ineffective carrier of O_2.
    - Normally, some methemoglobin (i.e. hemoglobin with $Fe^{+++)}$ production develops in the body (up to a few % of the total hemoglobin)

  - Small amounts of methemoglobin are reduced to the normal, fully functional hemoglobin molecule (i.e. with Fe^{++}) by the enzyme NADH methemoglobin reductase.
- Examples of agents that cause oxidative injury to RBCs (potential for Heinz bodies and serious methemoglobinemia):
  - Rape, kale, turnips (*Brassica* spp.): deplete glucose-6-phosphate dehydrogenase.
  - Onions and garlic (*Allium* spp.) also deplete this enzyme.
  - Red maple (*Acer rubrum*) leaves (green, red, brown, fresh or dried).
  - Acetaminophen (e.g. Tylenol ®) in domestic cats.
  - Nitrite (produced from nitrate, esp. in ruminants).
  - Chlorate (rarely used as a herbicide; in some matches).
  - Naphthalene (moth balls; some moth crystals) - probably oxidative .
  - Local anesthetics especially after oral administration.

Carbon monoxide (CO)

- CO has a much higher (245x) affinity for hemoglobin than does O_2.
- CO also decreases the tendency for hemoglobin to release to the tissues the oxygen being carried (with four binding sites, you have some sites carrying CO and other sites bearing O_2.
- Neonates and animals *in utero* are predisposed to CO toxicosis and associated hypoxic injury.

Methemoglobin Producers

V. Beasley

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Acetaminophen

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Methemoglobin Producers
Cats, dogs	4 - 24 hours	Days; highly lethal	

Sources

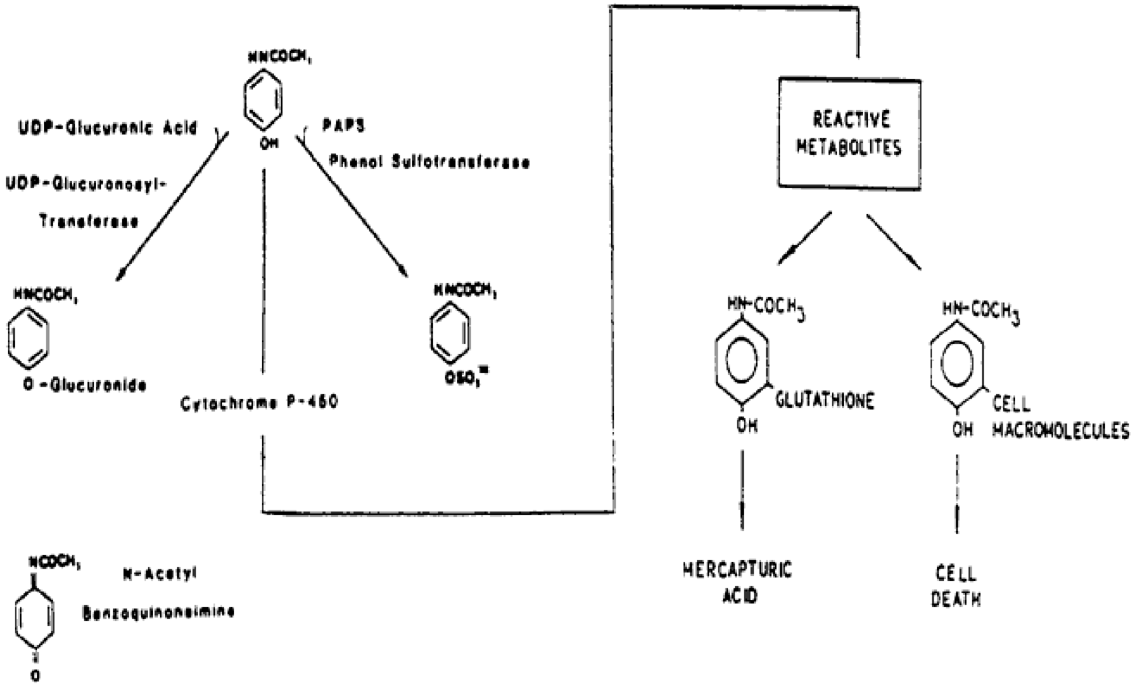
- Many "aspirin-free" pain relievers contain **acetaminophen**, e.g., Allerest, Anacin-3, Comtrex, Datril, Dristan-AF, Excedrin, Nyquil, Sinarest, Sine-Aid, Sine-Off, Sinutab, Tylenol, Vanquish, many others.
- Some analgesics contain **phenacetin**, which is **rapidly metabolized to acetaminophen**.

Absorption, Distribution, Metabolism and Excretion (ADME)

Rapidly absorbed from the gastrointestinal tract. Most is absorbed within 60 minutes. Previous ingestion of a high carbohydrate diet may delay gastric emptying so that peak plasma levels may occur as late as 4 hours after ingestion.

Mechanism of Action

- Two major conjugation pathways are used by most species for metabolism. Both involve P-450 metabolism, and for a major fraction of the compound, this is followed by glucuronidation or sulfation.
- Reactive metabolite from P-450 system can be conjugated by 1 of these 2 means or:
    - Be conjugated with glutathione - probably becomes toxicologically inert.
    - Bind to cellular macromolecules - causing cell dysfunction and/or cell death.



Major pathways of acetaminophen biotransformation. Adenosine 3'-phosphate 5'-phosphosulfate (PAPS), uridine diphosphoglucuronic acid (UDP-glucuronic acid), and uridine diphosphoglucuronosyltransferase (UDP-glucuronosyltransferase).

- Man, dogs, and cats have low ability for sulfation.
- Cats lack the specific glucuronyl transferase required to conjugate acetaminophen.
    - Reactive metabolites form.
    - Endogenous hepatic glutathione is quickly exhausted.
    - When glutathione levels drop to 20 - 30% of normal, metabolites bind to cells causing cell death.

Species Susceptibility

- Dogs and man.
    - Tolerate normal therapeutic dosages.
    - Usually no clinical signs are observed until dosage exceeds 100 mg/kg.
    - Signs are mainly referable to acute hepatic damage.
    - Three of four dogs exposed to acetaminophen at 200 mg/kg developed clinical methemoglobinemia.
- Cats.
    - **Acetaminophen-Containing Products Should Never Be Administered To Cats!!**
    - Lower dosages produce toxicosis, especially if the dose is repeated. Signs are largely referable to methemoglobinemia. Cats also develop liver lesions when poisoned by acetaminophen.
    - An oral dose of 60 mg/kg produced 21.7% methemoglobin 4 hours after administration.
    - Problems may be noted in cats exposed to as low as 40 mg/kg.

Signs and Lesions

- Cats.
    - Cyanosis.
    - Methemoglobinemia. Specific quantitation of the percent hemoglobin is preferred. A screening assay can be performed by putting a drop of blood on a piece of absorbent white paper. A chocolate brown color generally indicates at least 15% methemoglobin.
    - Dyspnea.
    - Severe depression/weakness.
    - Anorexia.
    - Vomiting.
    - Facial and/or paw edema (mechanism not understood).
- Dogs and man.
    - Acute centrilobular hepatic necrosis usually 24 - 36 hours postingestion. Manifestations may include anorexia, vomiting, abdominal pain, shock, etc.

Treatment

- Goals:
    - Prevent absorption from the gastrointestinal tract with an emetic, activated charcoal, and a cathartic (because of rapid absorption, such measures are likely to be of benefit only for very recent ingestions, i.e., < 2 hours).
    - Do not use an emetic if animal is hypoxic.
    - Intercept reactive metabolites and promote their excretion.
    - Convert methemoglobin (reduce it) back to hemoglobin (in cats).
    - Support cardiovascular/respiratory system function.
    - Activated charcoal and a cathartic (if appropriate as mentioned under goals above and under acetylcysteine below).
- Activated charcoal may possibly absorb and inactivate orally administered N-acetylcysteine (this is an area of controversy): **for now, do not give together**.
    - N-acetylcysteine is highly effective as a therapy for acetaminophen toxicosis.
    - N-acetylcysteine provides sulfhydryl groups, directly binds to acetaminophen metabolites to enhance elimination, and serves as a glutathione precursor.
    - For severely poisoned animals, initially give 280 mg/kg PO or IV in 5% dextrose (for milder cases, you can start with 140 mg/kg). If the IV route is used, the dose is given slowly over a period of 15 - 20 minutes. The IV route should be chosen if an emetic is to be used or if activated charcoal is still present in the upper gastrointestinal tract. For IV use, it is preferred to filter the acetylcysteine solution through a 0.2 micron filter. Most pharmacies will be able to provide a suitable bacteriologically filtered solution.

  - Follow with 70 mg/kg PO QID for a total of 6 doses after the loading dose (monitor as withdraw to assure that this course of therapy is long enough).
  - For most cases of acetaminophen toxicosis, acetylcysteine is best given solely by the oral route.
- More of acetylcysteine will reach liver if administered as oral dose.
- Sources:
  - Generic acetylcysteine of 98% purity from chemical company - 14% suspension in distilled water.
  - Mucomyst ® (Mead, Johnson, and Co.).
    - Sterile 10% and 20% solutions.
- As an alternative to acetylcysteine, sodium sulfate at 50 mg/kg has been evaluated after being given every 4 hours for a total of 3 doses (given IV as a 1.6% solution). Although significant benefit was apparent and the sodium sulfate was essentially equivalent to 3 doses of acetylcysteine (140 mg/kg, 70 mg/kg, 70 mg/kg), hepatic lesions were noted in both antidote treated groups. These results may suggest that treatments for longer periods of time (see above) are warranted.
- Ascorbic acid (20 mg/kg) up to QID - oral or parenteral.
  - Empirically recommended in an effort to convert methemoglobin to oxyhemoglobin.
  - Ascorbic acid is safe for cats (at doses recommended for acidification of the urine).
- Supportive fluid therapy.
- If **severe** cyanosis is present, supply oxygen.
- Cage rest.
- Steroids and antihistamines are **contraindicated!!**

N-acetylcysteine sources

1. Fisher Scientific Company.*
   1600 Glenlake Road, Itasca, IL 60143.
   *An account is required for purchasing. Application required for first time orders.
   Cost: 25 grams (powder concentrate), 100 grams
   Observe precautions for storage, handling, and administration.
2. University of Illinois, Veterinary Medicine Pharmacy. 20% solution, in stock
   4 ml vials
   10 ml vials
3. Redbook prices. Mead-Johnson, Mucomyst ®.
   10%
   4 cc each x 12 vials
   10 cc each x 3 vials
   30 cc each x 3 vials
   20%
   4 cc each x 12 vials
   10 cc each x 3 vials
   30 cc each x 3 vials
4. Local hospital or pharmacy.
   Prices will vary
   Most practical and fastest to obtain
   20% solution may be most cost-effective.
   Carle Pharmacy, Urbana:
   20% - 10 ml x 3 vials/pack
   10% - 10 ml x 3 vials/pack

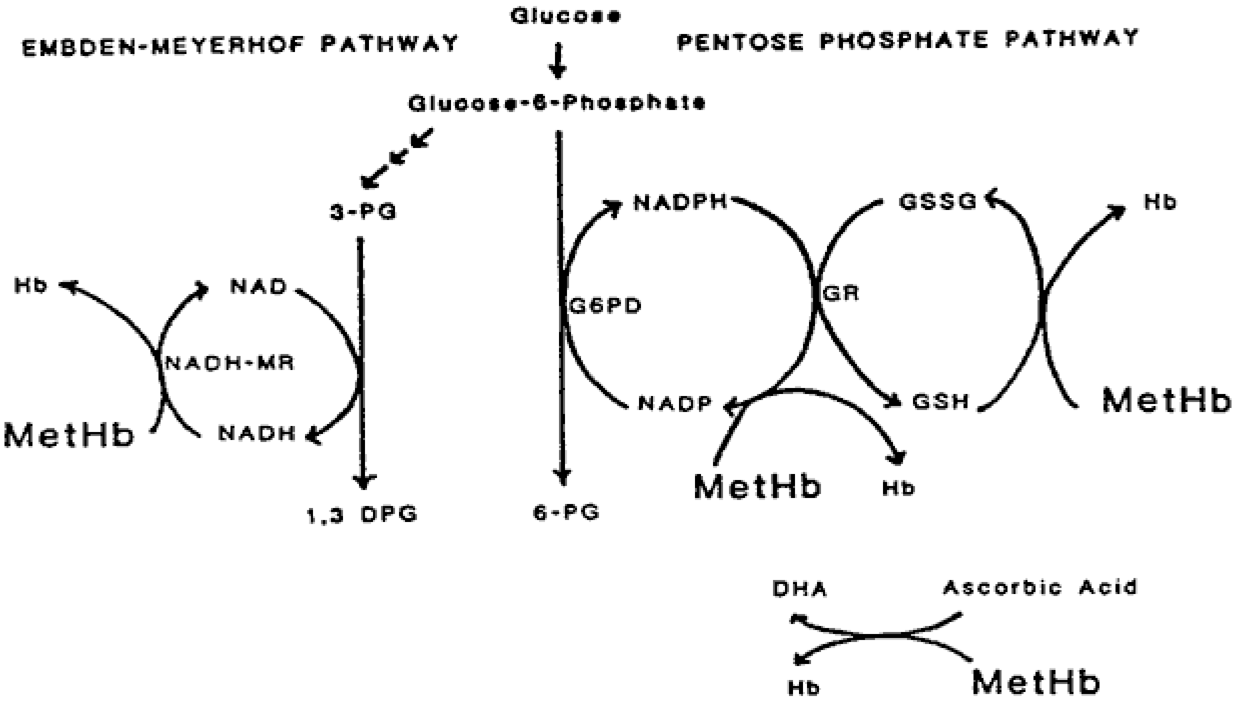
Case Example:

a. A 5-kg cat, presented with severe complications:
   Loading dose (maximum at 280 mg/kg) 1400 mg
   Maintenance dose (350 mg x 6 doses) 2100 mg
   Total needed 3500 mg
b. Using:
   10% solution, 10 ml vial
   requires 3.5 vials (4 vials)

   20% solutions, 10 ml vial
   requires 1.5 vials (2 vials)

Weight-Dosage Conversion Chart N-Acetylcysteine (Mucomyst ®)									
					Maintenance Dose				
		Loading Dose							**Total Needed mg**
Animal Weight		**mg**	**% Solution**		**mg/dose**	**Total mg (6 doses)**	**% Solution**		
kg	**(lb)**		**10**	**20**			**10**	**20**	
1	(2.2)	140	1.4 ml	0.7 ml	70	420	0.7 ml	0.35 ml	560
2	(4.4)	280	2.8 ml	1.4 ml	140	840	1.4 ml	0.7 ml	1120
3	(6.6)	420	4.2 ml	2.1 ml	210	1260	2.1 ml	1.05 ml	1680
4	(8.0)	560	5.6 ml	2.8 ml	280	1680	2.8 ml	1.4 ml	2240
5	(11.0)	700	7.0 ml	3.5 ml	350	2100	3.5 ml	1.75 ml	2800
6	(13.2)	840	8.4 ml	4.2 ml	420	2520	4.2 ml	2.1 ml	3360
7	(15.4)	980	9.8 ml	4.9 ml	490	2940	4.9 ml	2.45 ml	3920
8	(17.6)	1120	11.2 ml	5.6 ml	560	3360	5.6 ml	2.8 ml	4480
9	(19.8)	1260	12.6 ml	6.3 ml	630	3780	6.3 ml	3.15 ml	5040
10	(22.0)	1400	14.0 ml	7.0 ml	700	4200	7.0 ml	3.5 ml	5600
20	(44.0)	2800	28.0 ml	14.0 ml	1400	8400	14.0 ml	7.0 ml	11200
30	(66.0)	4200	42.0 ml	21.0 ml	2100	12600	21.0 ml	10.50 ml	16800
40	(88.0)	5600	56.0 ml	28.0 ml	2800	16800	28.0 ml	14.00 ml	22400
50	(110.0)	7000	70.0 ml	35.0 ml	3500	21000	35.0 ml	17.50 ml	28000

1. Mucomyst ® (N-acetylcysteine), Mead-Johnson.
2. Available Forms:
   - in packs of 3 - 10 ml vials
   10% solution
   20% solution
3. Each 10 ml vials contains:
   10% solution - 1000 mg N-acetylcysteine (100 mg/ml)
   20% solution - 2000 mg N-acetylcysteine (200 mg/ml)
4. Loading and maintenance doses determined from protocol, i.e., loading dose of 140 mg/kg (280 mg/kg in severe clinical situations), followed by maintenance dose of 70 mg/kg every 6 hours for a total of 36 hours (7 treatments).
   Note - Do not administer N-acetylcysteine orally with activated charcoal.



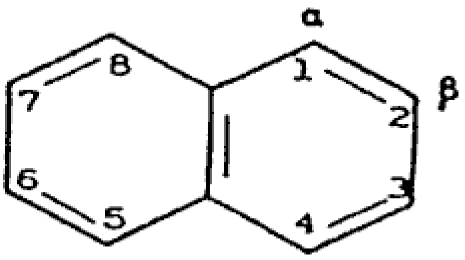
Pathways in the reduction of methemoglobin.
Abbreviations: Met HB = methemoglobin; Hb = hemoglobin; NADH-MR = NADH-dependent methemoglobin reductase; PG = phosphogluconate; DPG = diphosphoglycerate; GSSG = oxidized glutathione; GSH = reduced glutathione; GR = glutathione reductase; DHA = dehydroascorbic acid.

Naphthalene

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Methemoglobin Producers
Dogs, cats	Hours	Days; often lethal	

Sources

- Naphthalene is present in "old-fashioned" mothballs. It is the most common active agent in mothballs. Naphthalene is also present in some types of mothflakes or crystals; but in these products, paradichlorobenzene may be used more often.
- Example - Enoz Old Fashioned mothballs contain 2.7 grams of naphthalene per mothball.
- Naphthalene mothballs are approximately 2 times as toxic as paradichlorobenzene mothballs, the only other commonly encountered type.



Naphthalene

Toxicity

- Naphthalene appears to be quite toxic to cats.
- Less than one naphthalene mothball may induce toxicosis in a child.
- Acute hemolytic anemia has been reported in dogs at 411 mg/kg or greater.

Signs and Clinical Pathology

- GI irritation, vomiting may account for the most common complaints.
- Methemoglobinemia.
- Heinz body anemia associated with hemolysis; accounts for majority of serious effects.
- Hemoglobinuria.
- CNS abnormalities (possible seizures) are infrequently seen.
- Rarely, hepatitis occurs 3 - 5 days postingestion.

Treatment

- Emesis.
- Activated charcoal.
- Saline cathartic.
- Control methemoglobinemia.
    - In cats and usually in dogs, use ascorbic acid at 20 mg/kg.
    - In other species use methylene blue.
    - Low doses of methylene blue (1.5 mg/kg) have recently been reported to be beneficial to cats with nitrite-induced methemoglobinemia. Methylene blue given in the absence of methemoglobinemia can cause Heinz body formation.
- For animals with hemolytic crisis, fluids and bicarbonate (2 - 3 mEq/kg slow IV added to fluids over a period of hours), are suggested to minimize precipitation of hemoglobin in the kidney and associated nephrosis.
- For anemic animals, a blood transfusion may be of value.
- Control seizures.
- Supportive care.

	Paradichlorobenzene	**Naphthalene**
Surface appearance	wet, oily	dry
In ethanol	rapidly soluble	slowly soluble
In 60ºC water	soluble	insoluble
Reaction with chloroform, aluminum chloride, anhydrous powder	no reaction	intense blue color
Reaction with copper wire in a flame	bright green flame	no color
Immersion in a saturated solution of table salt	sink	float

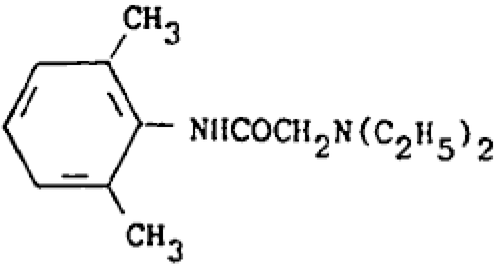
- Simple specific gravity method to differentiate type of moth balls. Test for **sink** vs. **float**: start with 4 ounces of tepid water. Add 3 heaping tbsp of table salt. Stir vigorously until salt will not further dissolve.
    - Naphthalene mothballs - **Sink** in water, but **float** in saturated salt solution
    - Paradichlorozene mothballs - **Sink** in water, and **sink** in salt solution.
    - Apparently this is a very reliable test.

Local Anesthetics

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**	Full Table for Methemoglobin Producers
Local Anesthetics	Most species	Hours	Hours to a day; often lethal	
Resorcinol in cats	Mostly cats	Hours	Days; often lethal	

Sources

- Local anesthetic preparations including lidocaine, benzocaine, and tetracaine are present in a variety of preparations for topical use. These include mucosal sprays, suppositories, nonprescription cremes, teething gels, and aerosols.
- They are used to facilitate endotracheal intubation, especially in the feline animal in an effort to control laryngeal spasm.
- Xylocaine ® contains lidocaine.
- Cetacaine ® contains benzocaine and has been recommended for use as a laryngeal or pharyngeal spray to control pain or gagging. Some veterinarians have suggested its use locally in the urethra in attempts to relieve feline urologic syndrome. These uses are not without risk.
- Lanacane ® cream and Bicozene ® contain 6% benzocaine and resorcinol, and Vigisil ® contains 5% benzocaine and resorcinol. These products are available in 1 oz (30 g) or 2 oz (60 g) tubes.



Lidocaine

Susceptible Species

- Humans, dogs, and cats have all been poisoned by local anesthetics.
- Cats are well recognized as the domestic species having hemoglobin most susceptible to the action of oxidizing agents, including aromatic amines.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanism of Action

- Local anesthetics or, more likely, their metabolites cause oxidation of hemoglobin to produce methemoglobin and cause Heinz body formation.
- Local anesthetics contain a common aromatic group connected via an intermediate chain to an amino group by either an amide or an ester linkage. Of the local anesthetics which have been implicated in the formation of methemoglobin, lidocaine and prilocaine contain amide linkages. These bonds are metabolized slowly by liver microsomal enzymes, resulting in intermediates which are believed to act as oxidants.
- In cats, an injection of prilocaine or o-toluidine, its proposed metabolite, induced approximately equal levels of methemoglobinemia. In the same study, however, both lidocaine and its proposed metabolite, 2,6-xylidine, failed to produce methemoglobinemia in cats, suggesting an alternate mode of metabolism or, at least, lesser susceptibility to this local anesthetic in the cat.
- Benzocaine contains an ester bond and is metabolized by esterases in the plasma. However, the specific metabolite responsible for its effect on hemoglobin is unknown.

- Conjugation of local anesthetics is a necessary step prior to their elimination in the urine. The deficiency of glucuronyl transferase in cats may contribute to their susceptibility to benzocaine and other oxidant drugs.
- Benzocaine is one of the least water-soluble local anesthetics, a factor which reportedly slows its absorption. The Cetacaine ® preparation, however, contains preservatives which are reportedly irritating to the mucous membranes. This irritation may, along with any pre-existent laryngeal lesions, increase absorption.
- Whether instillation into the trachea increases the fraction absorbed, as compared to oral exposure, remains to be experimentally documented.
- Additional properties of local anesthetics which are **less often** associated with clinical toxicoses include:
    - Cardiac effects: interference with intraventricular conduction, myocardial contractility, and electrical excitability, resulting in arrhythmias. Hypotension and cardiac arrest can occur.
    - Direct vasodilation may result in hypotension.
    - At low doses local anesthetics are anticonvulsants, and at high doses they are convulsants.
    - Respiratory effects: depression and apnea can also occur.
    - Nervous effects: may include seizures, tremors, agitation, lethargy, and coma.
    - Acidosis may also be observed.

Toxicity

- Similar metered sprays of Cetacaine ® (benzocaine) or Xylocaine ® Spray (lidocaine) were administered to cats. When cats were treated with a one-second spray of Cetacaine ® (8.1 mg benzocaine), the animals consistently experienced significant methemoglobinemia (up to 30%), while a similar exposure to Xylocaine ® Spray (10 mg lidocaine) had no such effect.
- In spite of the absence of an effect in this study, it has been noted that lidocaine-metered sprays, intended for human patients, do deliver a greater and, therefore, excessive dose for cats.
- An appropriate method of laryngeal treatment would be the use of a 1 - 2% solution on a cotton swab, applied directly to the laryngeal folds.
- Cats intravenously dosed with benzocaine at up to a total dose of 41 mg (2.1 mg/kg) developed methemoglobinemia up to a high value of approximately 22%.
- Dogs are sometimes clinically poisoned by ingestion of ointments or cremes containing local anesthetics.
- Methemoglobinemia has been experimentally produced (at up to 14%) in dogs intubated with endotracheal tubes to which a gel containing 20% benzocaine was applied.

Signs

- In experimentally treated cats, methemoglobinemia developed within 5 - 10 minutes of a one-second laryngeal spray of Cetacaine ® (benzocaine) and peaked at 20 - 30 minutes after application. Two of the 7 treated cats developed clinical signs of cyanosis.
- Elevated values of methemoglobin persisted 30 minutes to 3 hours.
- Had greater degrees of exposure been tested, more severe effects would have been likely.
- Cyanosis, rapid, shallow respiration, and prolonged sedation may also occur.
- It was reported that the peripheral veins of Cetacaine ®-treated cats were difficult to palpate and visualize following treatment.

Diagnosis

- Normal methemoglobin is reported as approximately 1% in cats.
- Diagnoses are based upon the presence of significant methemoglobinemia and/or a Heinz body anemia, a history of excessive exposure to a local anesthetic, and absence of exposure to other oxidants (especially acetaminophen in the cat).

Treatment

- For very recent oral exposure, in patients in which contraindications do not exist, an emetic may be used, and in any case, activated charcoal and a saline cathartic are suggested.

- Diazepam is suggested for seizures in dogs. Phenobarbital is suggested if diazepam fails to control the seizures. Phenobarbital is suggested for other species if seizures occur. If phenobarbital fails, pentobarbital is suggested.
- For acidosis, sodium bicarbonate in fluids is suggested.
- Forced diuresis has been shown to be of benefit for some local anesthetics but may not be of benefit for others.

For Methemoglobinemia

- Ascorbic acid:
    - Ascorbic acid (vitamin C) has been suggested to correct methemoglobinemia at a dose of 20 mg/kg. However, controlled studies of its effectiveness remain to be conducted.
- Methylene blue:
    - It is best to avoid the use of methylene blue in the dog unless absolutely necessary (i.e., if vitamin C fails to provide sufficient benefit.
    - When given to the dog, the recommended dose of methylene blue is 4 mg/kg. There is little available data on which to base this recommendation, and it is reported that a dose of methylene blue at 10 - 15 mg/kg can cause acute intoxication and death in dogs due to hemolytic anemia with Heinz body formation.
    - Low doses of methylene blue (1.5 mg/kg) have recently been reported to be beneficial to cats with nitrite-induced methemoglobinemia. Methylene blue given in the absence of methemoglobinemia can cause Heinz body formation.
- Oxygen:
    - Oxygen therapy may be of limited benefit after the administration of agents intended to reduce methemoglobin back to hemoglobin.

Nitrate - Nitrite

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Methemoglobin Producers
Nitrate and nitrite	Ruminants, occasionally other species	Minutes to hours	Hours to 2 days; often lethal	
Nitrate-accumulating plants, e.g.:	Ruminants, occasionally other species	Hours to days	Hours to 2 days; often lethal	
Sorghum (*Sorghum*), Sudan grass	(See Cyanogenic Glycoside-Containing Plants)			
Corn, especially green chop (*Zea mays*)				
Oats (*Avena sativa*)				
Wheat (*Triticale*)	-			
Beets (*Beta*)	(See Toxicants that Affect the Kidneys)			
Kochia	(See Poisonous Plants that Affect the Liver)			
Locoweeds (organic nitrates)	(See Toxicants with Mixed Effects on the CNS)			
Fiddleneck (*Amsinckia*)	(See Poisonous Plants that Affect the Liver)			
Fescue (*Festuca*)	(See Toxicants that Affect Peripheral Circulation) (Methemoglobinemia is rare)			
Pigweed (*Amaranthus*)	(See Plants that Affect the Kidneys) (Methemoglobinemia is rare)			
Lamb's quarters (*Chenopodium*)	(See Plants that Affect the Gastrointestinal Tract) (Toxicosis is rare)			
Many others	-			

Sources

Nitrate-Accumulating Plants	
Sudan Grass (*Sorghum* spp.)*	Sweet Clover (*Melilotus*)
Johnson Grass (*Sorghum* spp.)*	Flax, linseed (*Linum*)
Sorghum (*Sorghum* spp.)*	Pigweed (*Amaranthus*)
Fireweed (*Kochia*)*	Lambsquarters(*Chenopodium)*
Beets (*Beta*)*	Canada Thistle (*Cirsium*)
Rape (*Brassica*)*	Jimson weed (*Datura*)
Corn (*Zea*)*	Wild Sunflower (*Helianthus*)
Rye (*Secale cereale*)	Cheeseweed (*Malva*)
Wheat (*Triticum*)	Smartweed (*Polygonum*)
Oats (*Arena*)	Dock (*Rumex*)
Fescue (*Festuca*)	Nightshades (*Solanum*)
Alfalfa (*Medicaqo*)	Soybeans (*Glycine*)

* Indicates plants of greatest risk.

- **Factors Increasing Nitrate Concentrations in Plants**
  - Species of plant (nitrate accumulators).
  - Heavy fertilization.
  - Factors that tend to reduce plant nitrate reductase activity):
    - Drought or rainy period after drought.
    - Decreased light (cloudy weather, early in the day before exposure to much sunshine). For these reasons, it is wise to cut hay or green chop relatively late on a sunny day to minimize concentrations of nitrate.
    - Decreased temperature.
- **Nitrates in Water**
  - Run-off from fertilized fields.
  - Run-off from decaying manure in barnlots.
  - Silage juices.
  - Nitrates or nitrites may leach through soil to deep and especially shallow, poorly cased wells.
  - Concentrations are less likely to be excessive in ponds with abundant plants or algae. Algae blooms decrease nitrates which decreases the risk of nitrate poisoning for exposed animals but (blue-green) algae is sometimes a worse hazard.
  - Concentrations may be highest after high surface run-off (heavy rains, spring snow melts), especially when recently applied fertilizer washes into small ponds or very small streams.
- **Fertilizers**
  - Some nitrogen fertilizers are high in ammonium nitrate.
  - Occasional sources for large animals (sodium, potassium, or ammonium nitrate).
  - May be eaten directly from bags, spilled, unevenly spread, or washed into water (see above).
  - Fertilizer is the primary source of nitrate for small animals.
  - Some nitrogen fertilizers are high in urea.
- **Time**
  - Concentrations in plants are generally highest just prior to flowering and rapidly drop off after pollenation occurs and grains or fruits set on.
  - There is evidence of postharvest reduction of nitrate to nitrite in feedstuffs such as moist hay and silage, a factor which could increase toxicity. Conversely, with completion of the ensiling process, nitrate-containing feeds often become somewhat less hazardous with conversion of the nitrite to ammonia and dissipation.
- **Drying**
  - Most nitrate is **retained when plants are air-dried** at ambient temperatures (e.g., hays). The nitrate content of hay may even increase during storage due to moisture loss.
  - Acid soils.
  - Low molybdenum, sulfur, phosphorus, manganese, or magnesium in soils.
  - Application of phenoxy (2,4-D like) herbicides.
  - Nitrates accumulate in the vegetative tissues of the plant, not in the fruits or grain. Concentrations are usually greatest in the stalk and less in the leaves.

Mechanisms of Action

- Nitrite is the actual toxic compound.
- Ruminants are much more susceptible to nitrates than monogastric animals.
- Rumen microorganisms reduce nitrate (NO_3) ion to nitrite (NO_2) ion.
- Nitrite oxidizes hemoglobin to methemoglobin.
    - 30 - 40% methemoglobin causes mild clinical signs.
    - 75 - 90% methemoglobin causes severe clinical signs to death.
- Fetuses and neonates are more susceptible than are the older young or the adults.
- The small quantities of methemoglobin formed during (normal) metabolism of physiologic amounts of nitrites or other oxidizing agents are converted to hemoglobin by an enzyme in erythrocytes, methemoglobin reductase. When the formation of methemoglobin exceeds the turnover rate of methemoglobin reductase, abnormally high concentrations of methemoglobin will occur.
- Vitamin A deficiency may be an effect of nitrate toxicosis and contribute to the occurrence of abortion (but this is only a theory, it has not been substantiated).

Toxicity

- Acute nitrate poisoning is most likely to occur when forage nitrates exceed 10,000 ppm (1%) (dry weight basis) or when water contains 1500 ppm (0.15%) nitrate. Since the effects of feed and water nitrate are additive, both should be tested when the probability of toxicosis is being evaluated.
- Lethal doses of nitrate and nitrite are included in the following table:

Source Species	**Lethal Dose in mg/kg of body weight**
Nitrate	
Adult humans	80 - 130
Cattle	330 - 616
Sheep	308
Sodium Nitrite	
Adult humans	110 - 165
Rabbits	80 - 90
Pigs	90
Sheep	170

- The amount of preformed nitrite influences toxicity, especially in monogastric species.
- The susceptibility of an animal to nitrate toxicosis is dependent upon several factors including: **1**) rate of intake, **2**) variations in gastrointestinal nitrate reduction (adaptation), **3**) diet (nutrition), **4**) metabolic state of the animal as influenced by age, pregnancy, and disease.
- Nitrite reduction in the gastrointestinal tract is attributed solely to action of microorganisms. In ruminants, this reduction primarily occurs in the rumen; and nitrate, nitrite, and ammonium ions are absorbed directly into the blood.
- The inclusion of readily fermentable carbohydrates in the diet has been shown to protect ruminants against nitrate toxicosis.
- Pregnant ruminants should not be fed over 0.2% nitrates.
- In monogastric species, with the exception of the human infant, the stomach contains relatively few microorganisms due to the presence of hydrochloric acid. Monogastric species are, therefore, relatively resistant to toxicosis due to nitrates but are susceptible to poisonings by preformed nitrites.
- Human infants are more susceptible to nitrates and nitrites than adults. This appears to be due to differences in the gastric flora as a result of lower gastric acidity and the comparative ease with which hemoglobin of the fetus is converted to methemoglobin.
- Young rats and pregnant rats have also shown an increased sensitivity to nitrites.

Nitrate and Nitrite Expressions and Conversion Factors for Converting from One Way of Expressing Nitrate to Another					
Form A	Form B				
	N	NO_2	NO_3	KNO_3	$NaNo_3$
Nitrate-Nitrogen (N)	1.0	3.3	4.4	7.2	6.1
Nitrite-Nitrogen (N)	1.0	3.3	4.4	7.2	6.2
Nitrate (NO_3)	0.23	0.74	1.0	1.63	1.37
Nitrite (NO_2)	0.3	1.0	1.34	2.2	1.86
Potassium Nitrate (KNO_3)	0.14	0.64	0.61	1.0	0.84
Sodium Nitrate ($NaNO_3$)	0.16	0.54	0.72	1.2	1.0

To convert Form as Expression A to the equivalent amount of Form B, multiply A by the appropriate conversion factor. (Nitrate as Form A x Conversion Factor = nitrate as Form B.)

Feed Concentration as Nitrate Ion (Dry Matter Basis)	Estimated Toxicological Significance for Cattle
0.0 - 0.44%	Considered safe to feed under all conditions.
0.44 - 0.66%	Safe for nonpregnant animals under all conditions. Limit pregnant animals to 50% of the total dry matter in the ration
0.66 - 0.88%	Limit to 50% of the total dry matter in the ration
0.88 - 1.54%	Limit to 3 5 - 40% of the total dry matter in the ration. Feeds with over 0.88% nitrate ion should not be used for pregnant animals.
1.54 - 1.76%	Limit to 25% of the total dry matter in the ration. Do not use for pregnant animals.
Over - 1.76%	Feeds with over 1.76% nitrate ion may be toxic. Do not feed.

Source - Pennsylvania State University

Absorption, Distribution, Metabolism and Excretion (ADME)

- Both nitrate and nitrite are passively absorbed from the gastrointestinal tract and reach their highest concentrations 5 - 6 hours following their introduction into the rumen.
- In addition to conversion of nitrate to nitrite in the rumen, nitrate appears to be converted to nitrite by liver enzymes following absorption, but the rate of the hepatic reduction must be slow since no significant methemoglobinemia occurs following the intravenous administration of nitrates.
- Most nitrate is excreted by the kidney, but some is recycled back into the gastrointestinal tract by salivary and gastrointestinal tract secretion.

Signs

- Acute Syndrome (onset within 1/2 - 4 hours after feeding).
    - Direct gastrointestinal irritation - vomiting, salivation, diarrhea.
    - Dyspnea.
    - Tremors.
    - Ataxia.
    - Rapid, weak heart beat.
    - Terminal convulsions.
    - Death in 6 - 24 hours. The number of deaths is increased when animals are stressed due to increased oxygen requirements.

- Chronic Syndrome.
  Note - These are the results of field observations. Chronic toxicosis has not been experimentally reproduced. Other, unrecognized factors may be involved.
    - Abortions - "Lowland abortion syndrome". Some authors report that abortions may occur most often at 3 - 5 days after an acute toxicosis.
    - Poor growth and feed efficiency.
    - Decreased milk production.
    - Infertility.
    - Goiter, primarily in sheep (interference with iodine metabolism).
    - Increased susceptibility to infections.

Lesions

- "Chocolate-brown" blood.
- Brownish cast to all tissues.
- Agonal changes.
- Mucous membranes cyanotic.
- Congestion of ruminal or abomasal mucosae.
- Placental necrosis suggested by some authors.

Diagnosis

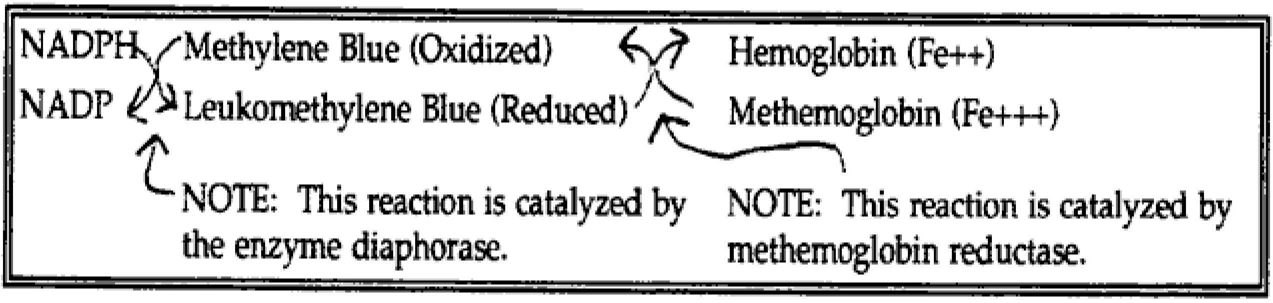
- Appropriate clinical signs and lesions.
- Laboratory analysis of nitrate and/or nitrite of: blood, serum, forages, feed, water, rumen contents, urine (NO_3 stable in urine for around 48 hours) and aqueous humor. Aqueous humor of aborted fetuses may also reveal elevated nitrate concentrations. Except for dry feeds, dry forages, and blood, specimens should be collected as rapidly as possible and shipped to the laboratory in a frozen state.
- Blood samples for methemoglobin analysis must be collected within 2 hours of death and rapidly frozen or preferably preserved in phosphate buffer to stabilize the methemoglobin (See Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Kendall/Hunt Publishing Company, 1984. - Available from amazon.com -).
- All samples should be shipped with as much air removed as possible.
- Results are reported in various ways (usually as NO_3, nitrate ion).
- Serum NO_3 of greater than 20 micrograms (µg) per ml is diagnostic.
- Fetal aqueous humor nitrate concentrations above 50 ppm have been deemed consistent with nitrate toxicosis and 30 - 50 ppm are considered suspect; thus when such levels are encountered diets and water also should be checked for nitrate.
- Field Analysis:
    - Diphenylamine test for nitrates.
    - Alpha-naphthylamine test for nitrites.

A Qualitative Field Test for Detection of Nitrate or Nitrite
Nitrate Screening Diphenylamine Test
1. Add 0.5 g diphenylamine in 20 ml of water.
2. Add sulfuric acid QS to 100 ml. Cool the resulting solution and store in a brown bottle.
3. Mix equal parts of the stock solution and 80% sulfuric acid.
4. Test suspect material by dropping 1 drop of reagent on the cut surface of the plant.
5. A color change from green to blue is a positive reaction indicating more than 2% nitrate.
Nitrite Screening Test
1. Reagents needed are **a**) sulfanilic acid (0.5 g in 150 ml of 20% glacial acetic acid) and **b**) alphanaphthylamine hydrochloride prepared by dissolving (with heat) 0.2 g of the salt in 20% glacial acetic acid.

2. Add 2 ml of unknown to a test tube. Then add 2 ml of sulfanilic acid, followed by 2 ml alphanaphthylamine. A pink to red color is positive for nitrites. The solutions applied to cut surfaces of plants in the same order will give a pink to red reaction if positive

Treatment

- Don't stress any more than necessary.
- Methylene blue.
    - 4 (dogs) to 15 (cattle) mg/kg IV in a 1% solution. Treatment may need to be repeated.
    - In preliminary studies, methylene blue has been used successfully and safely to treat nitrite toxicosis in cats. A single dose of 1.5 mg/kg IV can reverse methemoglobinemia much more rapidly than ascorbic acid or N-acetylcysteine without causing anemia. Multiple doses or a single dose in the absence of nitrite toxicosis, however, may cause Heinz body hemolytic anemia.
    - Avoid overtreatment since excessive doses of methylene blue may increase methemoglobin formation.
    - Dosage depends on severity.
    - Function of methylene blue:



NOTE: This reaction is catalyzed by the enzyme diaphorase.

NOTE: This reaction is catalyzed by methemoglobin reductase.

- Sources of methylene blue and diphenylamine: Sigma Chemical Co., Food and Drug Division, P.O. Box 14508, St. Louis, MO 63178, USA.

Toxicant	Blood Color	Mechanism	Treatment	Physical Characteristic
Nitrate (Nitrite)	Brown	Methemoglobin	Methylene blue	
Sodium Chlorate	Brown	Methemoglobin	Methylene blue	
Silo Gases (Nitrous Dioxide, Nitric Oxide)	Slight brown	Irritates deep portions of lungs; slight methemoglobin	Methylene blue; Ca gluconate	Heavier than air
Cyanide	Cherry red	Blocks cytochrome oxidases	Nitrite-thiosulfate	
Carbon Dioxide	Dark	Displaces oxygen	Oxygen; fresh air	Heavier than air
Carbon Monoxide	Bright red	Reduces ability of hemoglobin to carry O_2 (stable)	Fresh air; oxygen + 5% CO_2, thionine solution	Lighter than air

Prevention

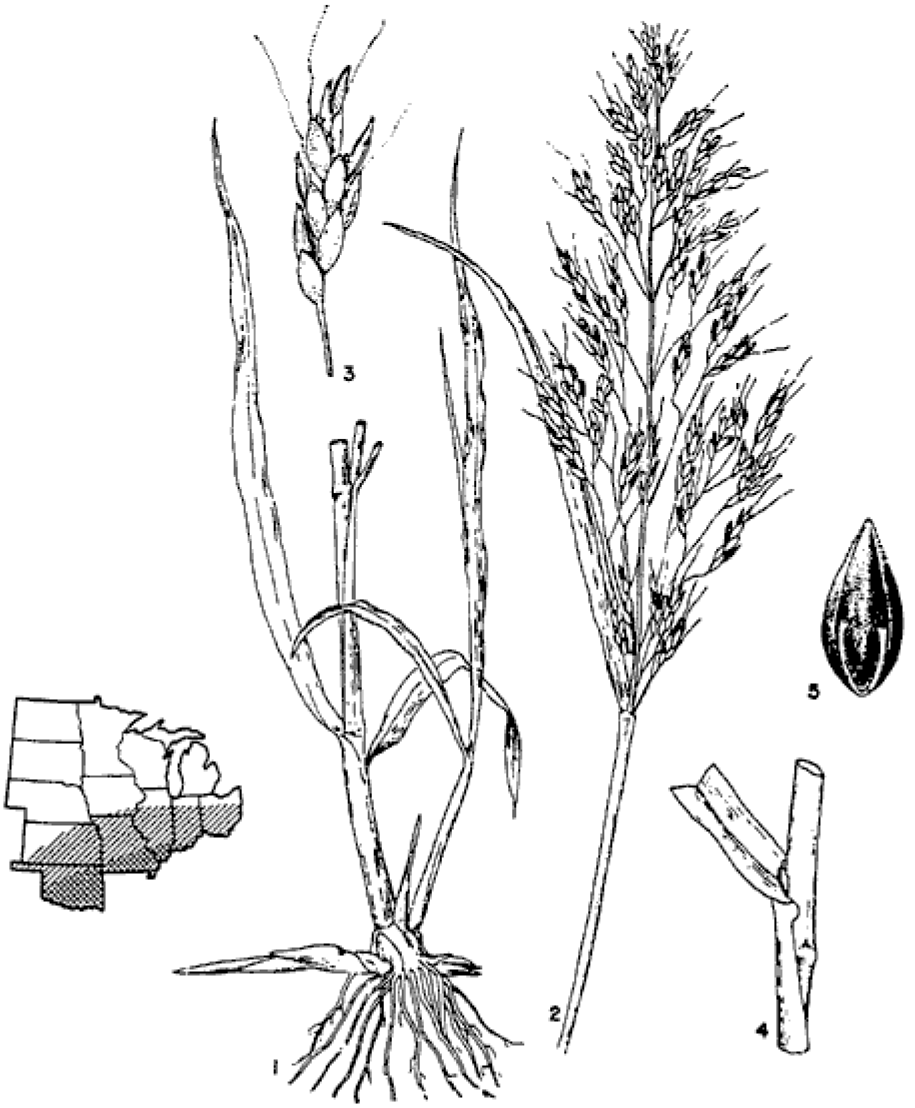
Forages

- Cut forage late in the day on a warm, sunny day.
- Analyze forage for nitrate **before** feeding suspect material.
    - A diphenylamine-based test for screening is available.
- Wait as long as possible before harvesting; nitrates decrease with maturity of plant.
- Wait at least 1 week prior to harvest following a rain which ended a drought.

- Harvest corn for silage rather than green-chop. Ensiling will decrease nitrates by 30 - 50% after 1 - 2 months.
- For each of the following, cut higher on the stalk: corn for silage or green chop, or forage for hay.
- Feed a grain supplement to increase the conversion of nitrates to protein.
- Dilute with feed known to be low in nitrate.
- If hay must be salvaged:
    - Grind hay and determine nitrate concentration.
    - Mix with good hay until concentration is no more than 0.5% nitrate.
- Supplement diet with vitamins A, D, and E and iodized salt.
- Animals should be well fed before their first access to suspect feed to decrease the initial amount consumed as a bolus.

Water

- Nitrate additions to ground water can be reduced by limiting nitrogen application, in the form of fertilizer and animal waste to amounts that can be taken up by plants. Soil type influences percolation and time of year is a factor in plant uptake.
- Wide green bands with abundant native plants tend to reduce runoff of nitrate into streams, ponds, and lakes.
- Nitrate can be reduced in water with ion exchange and reverse osmosis although an economic assessment is often necessary to determine whether this is a practical alternative.



Johnsongrass. *Sorghum halepense* (L.) Pers. **1**, stout stem base, roots, and a young rhizome; **2**, panicle; **3**, group of spikelets; **4**, section of stem showing base of leaf; **5**, seed. **Perennial**, reproducing by large rhizomes and seeds. **Root** system freely branching, fibrous. Rhizomes stout, creeping, with purple spots, usually with scales at the nodes. **Stems** erect, stout, from $1^{1/2}$ to 6 feet (0.45 to 1.8 m) or more tall. **Leaves** alternate, simple, smooth, 6 to 20 inches (15 to 50 cm) long, about 1/2 to $1^{1/2}$ inches (1.3 to 3.8 cm) wide. **Panicles** large, purplish, hairy. **Seed** nearly _ inch (3 mm) long, oval, reddish-brown, marked with fine lines on surface, bearing a conspicuous awn easily broken off. **Found** especially on rich soil. Troublesome in corn and soybeans on overflow bottoms. Difficult to control or eradicate. Listed as noxious weed in states where found.

Chlorates

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Methemoglobin Producers
All species	Hours	Hours to days	

Source

- Chlorate salts (usually sodium or potassium chlorate used as herbicides and defoliants, more commonly used in the past). Looks like salt, therefore can be accidentally mixed in feed.
- Careless disposal of chlorates.
- Mistaken use of chlorates for sodium chloride in animal feeds.
- Improper application of the dry salt with clumps of chlorate being left on ground.
- An average book of 20 matches contains 200 mg of potassium chlorate.

Toxicity

- According to Osweiler et al. (1985), the LD for most species is 0.5 - 1 g/kg; but for chlorate salts, Gosselin et al. lists the toxicity rating as 4 which translates into a potentially lethal dose of 50 - 500 mg/kg. Monogastrics and ruminants are of similar sensitivity.
- Chlorate decomposes in approximately 7 days in warm, moist soil.

Mechanism of Action

- Powerful oxidizing agent which converts hemoglobin (Fe II) to methemoglobin (Fe III).
- Chlorate is not inactivated in the reaction and continues to form methemoglobin until excreted - may also result in hemolysis.
- Chlorate is an irritant of the gastrointestinal tract.

Signs

- Onset often occurs within 1 hour. Since chlorates don't require reduction before they are active, the onset of action is faster than that observed in nitrates. This is the reason that monogastrics are just as sensitive as ruminants.
- Ataxia.
- Prostration.
- Hypersalivation.
- Purgation.
- Hematuria and hemoglobinuria.
- Cyanosis and dyspnea.
- Chocolate-brown blood
    - Methemoglobin.

Lesions

Dark brown tissues and blood, congested organs, blood-stained urine, erosions in stomach (abomasum) and duodenum.

Diagnosis

- Methemoglobin and history of chlorate exposure; chlorate determinations in plasma, urine, or aqueous humor.
- Differentials:
    - Nitrate/nitrite toxicosis.
    - Acetaminophen toxicosis in SA.
    - Local anesthetic toxicosis.

Treatment

- Gastric lavage.
- Intravenous administration of methylene blue at 4 mg/kg in dogs, 10 - 15 mg/kg in cattle using a 2 - 4% solution; may have to retreat - treat until blood no longer turns dark on standing. Low doses of methylene blue (1.5 mg/kg) have recently been reported to be beneficial to cats with nitrite-induced methemoglobinemia. Methylene blue given in the absence of methemoglobinemia can cause Heinz body formation.
- Vitamin C may be given to dogs and cats at 20 mg/kg. Low doses of methylene blue (1.5 mg/kg) have recently been reported to be beneficial to cats with nitrite-induced methemoglobinemia. Methylene blue given in the absence of methemoglobinemia cause Heinz body formation.

Prevention

- Remove animals from area treated with chlorates.
- If not feasible, give animals adequate salt intake at least 1 week prior to application and apply chlorates in form of a spray.
- Safety cannot be assured by this approach.
- Properly dispose of unused material.

Section XIX: Toxicants that Cause Hemolysis

Toxicants that Cause Hemolysis

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Red Maple (*Acer Rubrum*) Poisoning

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Hemolysis
Horses	1 - 6 days	Days; often lethal	

Source and Description

- Red maple is native to the entire eastern United States.
- Tree - Up to 120 feet tall.
- Growth Form - Medium size tree; trunk diameter up to 3 feet; crown oval or rounded.
- Bark - Gray and smooth when young, becoming darker and scaly.
- Twigs - Slender, mostly smooth, more or less reddish, usually with pale lenticels; leaf scars opposite, U-shaped, with 3 - 7 bundle traces.
- Buds - Rounded, reddish, usually hairy, up to 1/4 inch long.
- Leaves - Opposite, simple; blades up to 6 inches long, nearly as broad, palmately 3- to 5-lobed, the edges of the leaves sharply toothed to nearly toothless, pale green and smooth on the upper surface, white or gray and either smooth or hairy on the lower surface; leafstalks smooth or finely hairy, up to 4 inches long.
- Flowers - Staminate and pistillate borne separately, but sometimes on the same tree, in short dense clusters, bright red or yellow, opening in February and March before the leaves begin to unfold.
- Fruit - Borne in pairs, composed of an erect wing (or 2 wings) with a seed at the base, red or yellow, up to 1 inch long.
- Wood - Heavy, close-grained, light brown.
- Uses - Furniture, gun-stocks.
- Habitat - Swamps, low woods, upland slopes, bluff tops.
- Range - Newfoundland across to Ontario, south to eastern Texas, east to Florida.
- Distinguishing Features - The Red Maple is characterized by its white lower leaf surfaces and its shallowly lobed leaves. The similar Silver Maple has very deeply lobed leaves.

Toxic Principle and Mechanism of Action

> An, as yet, unidentified toxin creates an acute hemolytic anemia associated with methemoglobinemia and/or Heinz body formation.

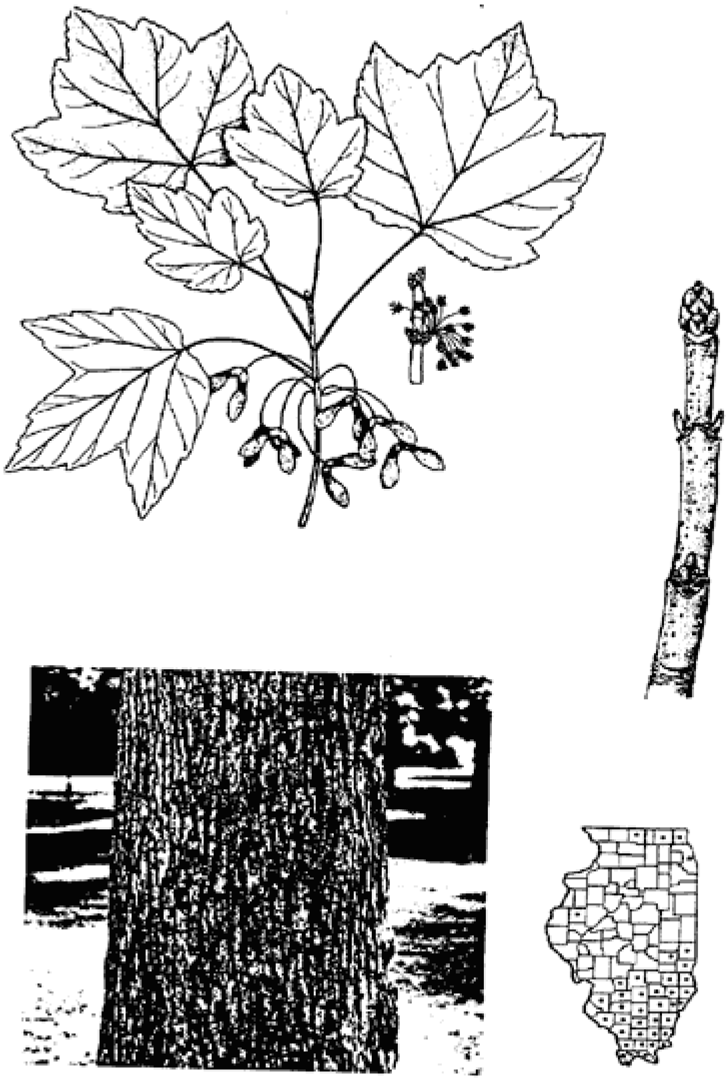
Toxicity

- Wilted or dried red maple (*Acer rubrum*) leaves are especially toxic.
- Overnight freezing and prolonged (4 weeks) storage does not destroy the toxic material.
- Ponies given dried red maple leaves at a dose of 3.0 gm/kg body weight became ill and died 1 - 5 days after administration.
- Ponies given dried leaves collected before September 15 became ill with a hemolytic crisis and died within 3 - 5 days. Ponies given dried leaves collected after September 15 died by 18 hours. This suggests there is a slight increase in the levels of toxin during the autumn.

Signs

- Depression, anorexia, dehydration.
- Icterus.

- Cyanosis.
- Slight increase in heart rate and respiration.
- Slight to severe anemia.
- Brown discoloration of blood (methemoglobin).
- Hemoglobinuria.



Red Maple (*Acer rubrum*)

Clinical Pathology

- Decreased packed cell volume.
- Increased white blood cell count.
- Methemoglobin.
- Heinz bodies.
- Increased SDH, bilirubin and CPK.
- Urinalysis.
    - Hemoglobin.
    - Increased protein.
- Methemoglobinuria.

Lesions

- Generalized icterus.
- Increased pleural and pericardial fluid.
- Ecchymoses on serosal surfaces.

- Splenomegaly.
- Hepatomegaly, pale centrilobular areas.

Differential Diagnosis

- Equine Infectious Anemia - Anemia.
- Babesia infection - Anemia.
- Phenothiazine poisoning - Heinz body formation.
- Cultivated and wild onion poisoning - Heinz body formation.
- Nitrite toxicosis - Methemoglobinemia.

Diagnosis

History of exposure and appropriate clinical signs. Recorded cases occur primarily from July to October, but may occur later.

Treatment

- Whole blood transfusion if necessary.
- IV fluids to prevent shock and dehydration.
- Continued saline diuresis may be necessary to prevent renal tubular nephrosis from the released hemoglobin. Added bicarbonate may facilitate this goal.
- Monitor renal function and serum electrolytes. **Note:**
    - Methylene blue may be **contraindicated** if methemoglobin exists and oxidation to Heinz bodies has already occurred. Methylene blue has been shown to be relatively ineffective in accelerating methemoglobin reduction in equine erythrocytes and also can cause significant Heinz body formation.
    - Ascorbic acid seems a logical therapy, but there are no known reports evaluating its use in *Acer rubrum* poisoning.

Prevention

- Prevent boredom and provide adequate nutrition (especially in fall and winter). This may decrease leaf eating.
- Remove trimmed branches or fallen limbs immediately after a storm.
- Prevent accumulation of leaves that fall or blow into horse pastures.

Onion (*Allium*) Poisoning

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Hemolysis
Dogs, cattle, other species	Hours to days	Days; potentially lethal	

Sources and Description

- The genus *Allium* includes various species of onion and garlic, including cultivated varieties.
- Cultivated (*A. cepa*) or wild (*A. validum*) onions as well as other species of onions (*A. canadense*), Egyptian garlic (*A. ampeloprasum*), and chives (*A. schoenoprasum*) have been implicated in poisoning of various species of animals.
- Ingestion of wild onion seldom causes signs of toxicosis.
- Livestock may be fed cull onions in areas where they are grown commercially. Often this can be done with few problems provided that they are mixed with ample amounts of other vegetable wastes or other feed components.
- Sometimes cool spring weather may delay growth of grass, whereas wild onions may readily propagate, making them the most readily available vegetation.
- A 12-kg dog was apparently poisoned after consuming the contents of a 3.5-oz jar of minced onions.

Toxic Principle and Mechanism of Action

- n-propyl disulfide is reported to be the toxic principle of *Allium* spp. and its only effects are on erythrocytes. The principle effects are related to hemolysis. This is believed to be secondary to oxidant-associated effects, and Heinz bodies may sometimes be evident.
- Other compounds are believed to be responsible for the lacrimator and antithrombotic effects associated with onions and garlic. Various sulfur-containing metabolites are probably responsible for the odors associated with ingestion of onions and garlic.

Susceptibility of Various Species

Cattle are more susceptible to onion poisoning than are horses, and sheep are even less susceptible, with goats being the least susceptible. In some cases, sheep may eat onions and show nothing more than slight hemoglobinemia. Poultry, rats, and rabbits have been experimentally poisoned.

Signs

- Discolored urine varying from port wine to almost black may be seen. Weakness, rapid breathing, and a rapid heart rate may be noted in hemolysis is sufficiently severe. Some animals may be icteric and/or have a characteristic onion odor to the breath.
- Loss of weight and appetite may occur. Severe toxicoses may be lethal.

Clinical Pathology

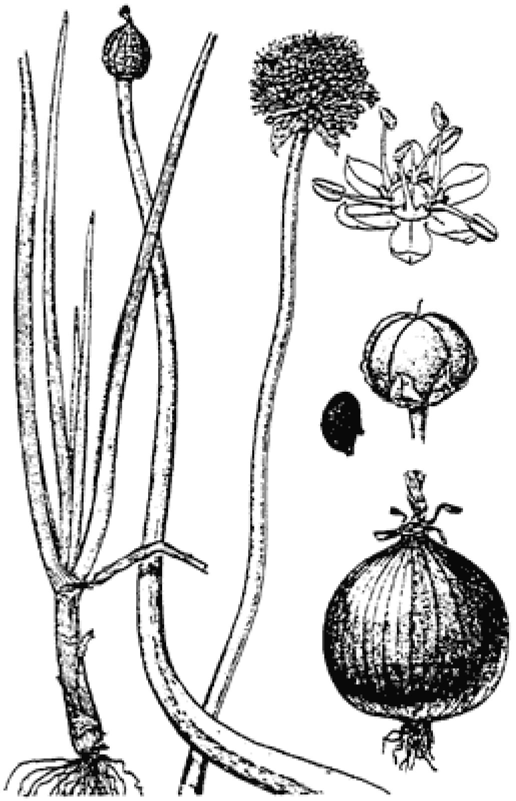
- Hemoglobinemia, hemoglobinuria, marked reductions in PCV. Heinz bodies sometimes reported.
- Evidence of damage of parenchymatous organs may be evident secondary to hemolytic anemia.

Differential Diagnoses

Include but are not limited to zinc toxicosis, copper toxicosis, autoimmune hemolytic anemia, and hemolytic blood parasites and bacterial infections.

Treatment

- Whole blood transfusion if necessary.
- IV fluids to control shock and dehydration.
- Saline diuresis with added bicarbonate (at least in animals with an acid urine) to limit hemoglobin-associated nephrosis.
- An empirical therapy to limit oxidant-induced damage of erythrocytes is ascorbic acid. There are no known reports of its use in this syndrome, however.
- Under some circumstances, methylene blue may be harmful to the horse (see section on Red Maple [*Acer rubrum*]) as well as to the dog. It is rarely recommended for felines. Low doses of methylene blue (1.5 mg/kg) have recently been reported to be beneficial to cats with nitrite-induced methemoglobinemia. Methylene blue especially when given in the absence of pre-existent methemoglobinemia) may cause methemoglobinemia and Heinz body formation.



Cultivated Onion.
The young green onion is shown on the left; the flower and seed stalks in the center; the enlarged flower, fruit, and seed in the upper right; and the onion bulb in the lower right of the drawing of this common food-seasoning plant.

Copper Toxicosis Copper Toxicosis-Molybdenum Deficiency Molybdenum Toxicosis-Copper Deficiency

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Hemolysis
Copper	Sheep, cattle, certain breeds of dogs	Hours to chronic	Days; often lethal	

Susceptibility

Because of major differences with regard to the sensitivity to copper toxicosis and the influence of molybdenum, this section is subdivided between species and syndromes. The most common and serious problem is copper toxicosis-molybdenum deficiency in **sheep**: an **acute syndrome** which suddenly occurs **after chronic dietary exposure to an excessive copper to molybdenum ratio**. **Cattle** are sensitive to an **excessively low dietary copper to molybdenum ratio**. **Goats** are 3 - 4 times more tolerant of copper than sheep. Genetic defects in some dog breeds (**Bedlington terriers**) cause excessive storage of copper in the liver eventually resulting in liver damage. All species are sensitive to excessive copper intake and are potentially affected by acute or subacute copper toxicosis.

1. Acute Copper Toxicosis

An acute syndrome of copper toxicosis results from ingestion or administration of copper containing formulations at a highly toxic dose.

Sources of Copper-Containing Compounds

- Anthelmintics
- Foot baths used for livestock (see below)
- Pesticides including fungicides and algicides

Toxicity

- There are marked differences among species in their ability to tolerate high levels of copper:
    - 30 - 50 ppm copper in the diet may be toxic to ruminants.
    - Dietary copper in excess of 250 ppm is required to cause toxic effects in swine and rats.
    - Sheep accumulate copper in the liver in proportion to intake.
    - Many nonruminants maintain normal liver copper levels until extremely excessive dietary levels are reached.
    - Copper sulfate added to diets at 125 ppm or higher may be lethal to rabbits.

Mechanism of Action

Possible coagulative necrosis of the gastrointestinal mucosa.

Signs

- Vomiting.
- Hypersalivation.
- Signs referable to abdominal pain.
- Diarrhea, often greenish tinged.
- Collapse and death sometimes occurs within 2 days.

2. Copper Toxicosis in Nonruminants

- Horses are comparatively tolerant of copper.
- Swine are comparatively tolerant of copper.
    - Dietary concentrations generally must exceed 250 ppm to cause toxicosis.
    - High dietary iron **and** zinc **protect** swine somewhat from the adverse effects of high copper levels. Similarly, **deficiencies of these elements increase susceptibility**.
    - **Signs** seen include anorexia, weight loss, weakness, melena, and death.
    - **Lesions** observed are pale livers with centrilobular necrosis, gastric ulcers, pale musculature, and "watery" blood.
    - Liver copper concentrations may be diagnostic.
- Poultry:
    - More resistant to copper toxicosis than most mammals.
        - **Turkey poults** reportedly tolerate 767 ppm in diet for 21 days.
        - **Chickens**: MLD of copper sulfate on mg/kg BW basis.

          Single crystal - 900
          Powdered - 300 - 500
          4% solution - 1,000 - 1,500

- Signs observed in toxicosis included weakness, anorexia, lethargy, anemia.
    - Dogs.
        - See Bedlington Terriers.

3. Chronic Copper Poisoning in Bedlington Terriers and Sometimes Other Breeds

Sources

Autosomal recessive defect causes increased copper retention in the liver which results principally in liver damage.

Mechanism of Action

Dark granules are observed in the liver, comprised of lysosomes containing copper and melanin. When the lysosomal capacity is overwhelmed, liver injury occurs.

Clinical Signs

- Three syndromes occur:
    - Young dogs, 6 years of age and less may exhibit:
        - Anorexia.
        - Vomiting.
        - Weakness.
        - Lethargy.
        - Dehydration.
    - These effects are believed to be due to active liver disease.
    - Older dogs, 6 - 12 years of age, may exhibit a chronic syndrome characterized by:
        - Anorexia, weight loss.
        - Occasional vomiting, diarrhea.
        - Jaundice.
        - Ascites.
        - Hepatic encephalopathy, death.
    - The third form is comparatively rare and consists of sudden, severe, hemolytic crisis and anemia.

Lesions

- Hepatomegaly or small liver.
- Prominent cytoplasmic granules in hepatocytes; focal hepatitis; focal cirrhosis; chronic, active hepatitis; generalized cirrhosis.

Diagnosis

- Breed - Bedlington terrier, West Highland white, Skye terrier.
- Lesions (liver biopsy).
- Affected dogs have liver copper concentrations usually of greater than 1,000 ppm on a dry weight basis and frequently over 2,000 ppm. The concentrations may increase with age up to a point and then decline but remain above normal.
- Normal liver copper in dogs (also on a dry weight basis) is approximately 90 - 350 ppm.
- Values above 350 ppm are considered diagnostic.
- The increase in SGPT occurs late and reflects hepatocellular injury.
- There is generally no increase in serum copper in affected dogs, except during an acute hemolytic episode.

Treatment

- Penicillamine (Cuprimine®), chronic administration.
- Glucocorticoids for lysosomal stabilization in acute disease.
- Ascorbic acid, 500 - 1,000 mg/day, to enhance urinary excretion of copper.
- 2,3,2-tetramine has been used as a chelator for copper in Bedlington terriers.

4. Subacute Copper Poisoning in Lambs

Sources

- In copper-deficient areas such as Florida, other southeastern coastal areas, and areas west of the Rockies, lambs are sometimes treated with copper-containing medications to prevent deficiency. A copper compound administered via oral drenching will often provide copper at a level adequate for several months. Single injections of copper-calcium EDTA or copper-methionate products may also be used.
- Even at the recommended rate of 50 mg copper, toxicosis may occur, especially in undersized lambs.

Lesions

- Gastrointestinal hemorrhage.
- Pulmonary edema.
- Ascites.
- Liver damage.
- Generally **no** icterus or hemolytic crisis.

Diagnosis

- Elevated serum, whole blood, liver, and/or kidney copper concentrations.
- History, lesions.

5. Copper Toxicosis/Molybdenum Deficiency

(Sometimes called chronic copper toxicosis. Primarily affects sheep and to some degree, young calves; much less often adult cattle).

Sources and Susceptibility

- Copper is routinely added to livestock mineral supplements and is a GRAS (generally recognized as safe by the FDA) feed additive.
- Molybdenum is not recognized by the FDA as an essential and safe element and its addition to feeds is thereby prohibited.
- Feeding to sheep of complete feeds intended for cattle or poultry can provide copper levels toxic to sheep.
    - Cattle can tolerate somewhat excessive copper and low molybdenum ratios, but sheep cannot.
- In the upper Midwest and Great Lakes states, diets containing the GRAS concentration of 15 ppm copper are often low in molybdenum so that 1 - 5% of sheep, may develop hemolytic crises.
- When a vitamin-mineral supplement is added to a ration, the copper concentration may be increased to 30 ppm or more.
- Natural molybdenum concentrations in rations are often 2 ppm or less.
- Consumption of forage plants naturally low in molybdenum and high in copper or confinement of sheep without green forage containing adequate molybdenum will skew the copper: molybdenum ratio.
- Complete rations for horses may be too high in copper for sheep.
- Consumption of plants contaminated by copper in pesticides such as bordeaux mixture (contains 1 - 3% copper sulfate) which is sometimes used in orchards.
- Water from ponds treated with copper containing algicides can cause toxicosis.
- Copper sulfate used as an anthelmintic or in solutions to treat infectious pododermatitis in ruminants can be a source of toxic levels of copper.
- Soils and vegetation contaminated from mining or smelting operations.
- Grazing on pastures amended by poultry or swine waste from animals fed copper-containing growth promotants.
- Grazing on vegetation growing on soils contaminated by copper mining or smelting operations.

Table 1
Copper Concentrations in Mineral Supplement Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory

Sample Number	Copper Concentration (ppm)	Sample Number	Copper Concentration (ppm)
1	5	9	115
2	7	10	115
3	8	11	125
4	28	12	180
5	40	13	212

6	70	14	240
7	73	15	330
8	76	16	440
Mean			110

Table 2
Copper Concentrations of Corn, Hay, and Complete Feed Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory. Results reported as parts per million (ppm).

Sample Number	Corn	Hay	Complete Feed
1	1.9	6.6	16
2	2.8	9.7	21
3	3.0	10.0	21
4	3.5		22
5	4.0		40
6	4.2		116
7	8.0		
Mean	4.0	9.0	40

Table 3
Molybdenum Concentration of Mineral Supplement, Corn, Hay, and Complete Feed Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory. Results reported as parts per million (ppm).

Sample Number	Mineral	Corn	Hay	Complete Feed
1	0.1	0.17	0.18	1.5
2	1.2	0.41	0.65	1.5
3	1.7	0.62	2.40	1.6
4	2.0	2.00		1.8
5	2.2			2.2
6	2.2			2.2
7				2.8
8				2.8
9				4.0
Mean	1.6	0.80	1.10	2.3

Note: The mean naturally occurring molybdenum content of feedstuffs is approximately 2 ppm or less.

Table 4
Copper: Molybdenum Ratios of Samples Submitted to the

University of Illinois Veterinary Diagnostic Laboratory	
Sample	**Copper:Molybdenum Ratio**
Complete Feed	18:1
Hay	8:1
Corn	5:1
Mineral Supplements	68:1

Toxicity

- The proper dietary ratio for sheep is 6 parts copper to 1 part molybdenum. Ratios in excess of 10:1 often result in clinical copper toxicosis in sheep.
- When normal dietary copper concentrations of 8 - 10 ppm and excessively low molybdenum concentrations of 0.5 ppm or less are present, an excessive buildup of copper and eventual hemolytic crisis may also occur.
- Copper sulfate is somewhat less toxic than many other copper salts, perhaps because of a sulfate-enhanced excretion of copper.
- Horse chow has been lethal to ewes.
- Copper in dry forages may be more available than copper from green forages.
- Toxicosis is often brought on by **stress**.

Absorption, Distribution, Metabolism and Excretion (ADME)

- **Absorption:**
    - Copper absorption takes place in the small intestine and, at least in sheep, considerable absorption also occurs in the large intestine.
        - Absorption varies as a function of the chemical form of the copper, the makeup of other minerals and organic materials in the diet, and the acidity of the intestine.
    - Most of the ingested copper is not absorbed and is therefore passed in the feces.
    - Copper absorption is poorly understood, but it is thought that a complex of copper with a protein, and another organic compound or another metal may be formed.
    - Zinc and copper may compete for the same carrier protein for transport across the intestinal mucosa into the blood.
    - Once absorbed, about 90% of the copper is firmly bound to a serum protein called ceruloplasmin and is loosely bound to albumin and amino acids.

- **Copper in the blood:**

    - Copper bound to ceruloplasmin is not as readily available for exchange or transfer as is free copper.
    - Copper in red blood cells exists primarily in 2 forms: 60% is in a superoxide dismutase enzyme called erythrocuprein and the remainder is loosely bound to other proteins.

- **Copper in the liver:**

    - When copper reaches the liver, the primary organ influencing its disposition, it is largely incorporated into the mitochondria, endoplasmic reticulum, nuclei, and cytosol of hepatocytes. The copper is either stored in these sites or released for incorporation into erythrocuprein, ceruloplasmins, or various copper containing enzymes.

- **Copper elimination:**

    - Copper is secreted into the bile and excreted into the intestine. Fecal excretion is the primary route of elimination, although most fecal copper is comprised of unabsorbed copper.
    - Small amounts of copper are also excreted in the urine.

- **Influence of molybdenum on copper disposition:**
  - *In vivo*, copper forms a complex with molybdenum in a molar ratio of 4:3, and the copper in this complex is biologically unavailable.
  - The copper-molybdenum complex may not prevent the intestinal absorption of copper, but it reduces copper accumulation in the liver.
  - The liver metabolizes considerable copper without ill effects provided that molybdenum and sulfate are present. Increased dietary concentrations of molybdenum and sulfate increase urinary and biliary excretion of copper. Molybdenum excretion is also promoted by sulfate. Molybdate inhibits the reduction of sulfate to sulfite, while copper antagonizes this effect of molybdenum.

- **Influence of liver damage:**
  - Plants or other toxicants that cause hepatic necrosis may impair the metabolism and excretion of otherwise tolerable amounts of copper.

Mechanisms of Action

- After copper builds up to about 150 ppm or more in the liver of sheep, the acute clinical syndrome of "chronic" copper toxicosis is initiated by the sudden release of copper from the liver into the blood. This may occur spontaneously, but it often seems to occur after some stress such as reduced feed intake, handling, or vigorous exercise. The copper content of blood is generally within the normal range until 24 - 48 hours before the onset of clinical signs, although an intermediate stage with a slight increase in blood copper may occur prior to the extreme release of copper.
- Generally, a sudden hemolytic crisis occurs, but not all animals that die of chronic copper toxicosis experience either hemolytic crisis or jaundice.
- Associated with the hemolysis is a marked reduction in red blood cell glutathione concentrations and an increase in methemoglobin, indicating that copper may, in some way, promote oxidative reactions that result in red blood cell destruction.
- Because of hemolysis, death may result from hemoglobin-induced renal damage and anemia.

Summary of the Mechanism of Action of Copper Toxicosis-Molybdenum Deficiency:

Copper buildup in liver from excess copper intake
(low molybdenum and low sulfate increase copper buildup)

Liver damage
+
Usually some stress factor
↓
Sudden release of copper
↓
Hemolysis, icterus, hemoglobinemia, hemoglobinuria
↓
Renal failure
↓
Collapse and death in 24 - 48 hours in most sheep

Clinical Signs

- Often excessive exposure has occurred for weeks or months before the onset of acute signs.
- Frequently a period of stress precedes the onset of signs.
- Sudden onset of weakness, trembling, anorexia, hyperventilation, hemoglobinuria (red or coffee-colored urine), and icterus are usually present.
- Occasionally only pale mucous membranes without icterus and hemoglobinuria are seen.
- Low morbidity generally (usually less than 5%), but mortality in affected animals is high (usually over 75%).
- If the syndrome progresses to death, the course generally lasts only 24 - 48 hours after the initial signs.

Clinical Pathology

- Liver enzymes such as SGOT, LDH, sorbitol dehydrogenase, arginase, and glutamic dehydrogenase may be increased for 6 - 8 weeks before the hemolytic crisis. The serum activities of these enzymes often return to near normal values 1 - 2 weeks before the hemolytic crisis, but increase to very high values shortly before or during the crisis.
- The enzyme activities do **not** correlate with copper concentrations in the blood.
- An increase in methemoglobin concentration may be seen.
- Hemoglobinemia, hemoglobinuria.
- Increased plasma bilirubin.
- Reduced PCV.
- Increased WBC, normal platelet counts.

Lesions

- Well before the hemolytic crisis, liver biopsies may show swelling and necrosis of isolated hepatocytes with swollen Kupffer's cells, rich in acid-phosphatase and containing PAS-positive, diastase-resistant material, and copper.
- Prior to the hemolytic stage, extensive proliferation of lysosomes is noted at the ultrastructural level in the hepatocytes of copper-dosed sheep.
- After the death of affected sheep, gross lesions usually include:
    - Generalized icterus.
    - Greatly enlarged gun-metal colored kidneys that sometimes are mottled with hemorrhage.
    - Slightly enlarged, friable, yellowish liver (or small, firm, pale liver).
    - Gallbladder distension with thick, greenish bile.
    - Splenic enlargement with a blackberry jam consistency and brown to black color in the parenchyma.
- Histologic changes include:
    - Cytoplasmic vacuolation and necrosis.
    - All liver lobules may contain clusters of necrotic cells.
    - Portal fibrosis begins early.
    - Renal tubules are clogged with hemoglobin with degeneration and necrosis of both tubular and glomerular cells.
    - The spleen is crowded with fragmented RBCs.
    - Status spongiosis has been reported in the white matter of the central nervous system.

Diagnosis

- Appropriate clinical history, signs, and lesions.
- Normal concentrations of copper in the blood range from 0.75 - 1.35 ppm. Concentrations above this range are often associated with copper poisoning. Often the concentrations are much higher at the onset of hemolysis.
- Normal liver copper concentrations in sheep range from 10 - 50 ppm (wet weight basis). Liver copper concentrations associated with copper toxicosis are usually greater than 150 ppm on a wet weight basis, whereas kidney concentrations are generally greater than 15.0 ppm.
- Complete sheep rations containing 25 ppm or greater with 2 ppm or less molybdenum may produce copper toxicosis. As noted under **Toxicity**, lesser amounts of copper may also be associated with toxicosis.
- In cattle, higher dietary copper concentrations may be necessary to induce toxicosis.

Treatment

- The prognosis for animals in the hemolytic phase of the disease is often poor. Usually the most benefit is derived via efforts to alleviate copper buildup in the rest of the flock.
- Urinary copper excretion is increased 10 - 20 times by the chelation agent, D-penicillamine, at 52 mg/kg/day for 6 days, although it may be prohibitively expensive for treating on a flock basis.
- Individual animals may benefit from alkalinization of the urine to decrease renal damage from hemoglobin. Animals may also improve in response to blood transfusions if serious anemia is present.
- Intravenous ammonium tetrathiomolybdate at 100 mg 2 times per week has been used to treat or prevent hemolytic crisis, minimize tissue damage, and decrease liver copper deposition.

- Supplementation of sheep rations with 2 - 16 ppm molybdenum has been efficacious in reducing the incidence of hemolytic crisis and in decreasing liver copper retention when sheep were fed copper at up to 45 ppm in the diet.
- Ammonium molybdate at 50 mg per head per day with 0.3 - 1 gram of thiosulfate daily for 3 weeks may help to prevent chronic copper toxicosis.
- Molybdenized superphosphate (at 4 oz molybdenum per acre) increases molybdenum content of pastures and reduces copper retention.
- Alternatively, molybdenized licks comprised of 190 lb salt, 140 lb finely ground gypsum, and 1 lb sodium molybdate may be used.
- Zinc may play a preventative role since supplementation of the ration with 250 ppm zinc as zinc oxide reduced liver copper buildup in lambs fed a ration containing copper at 40 ppm in the ration. The effect was synergistic with that of added sodium molybdate. Zinc at 175 - 375 ppm has also been shown to prevent hemolytic crisis in lambs fed copper at 29 ppm.

6. Excess Molybdenum-Deficient Copper (also see Molybdenum, Toxicants Affecting the Skin).

Cattle are more susceptible than sheep.

Sources

- Contamination of soils and forages in the vicinity of certain mining or smelting operations in which molybdenum containing ores are heated to high temperatures.
- Industrial contamination of farmland near metal alloy production plants.
- Contamination of soils with molybdenum containing fertilizers.
- In areas of Florida, other southeastern coastal regions, and in some states west of the Rocky Mountains (California, Oregon, Nevada), excessive molybdenum and/or deficient copper in soils and associated forages and grain may result in problems in cattle and, much less often, sheep.
- The critical copper to molybdenum ratio in cattle feeds is 2:1.

Toxicity

- When the ratio of copper to molybdenum in feed drops below 2:1, molybdenum toxicosis can be expected in cattle.
- Morbidity averages about 80% of the herd.
- When copper concentrations in feeds and forages are in the normal (8 - 11 ppm) range, cattle may be poisoned by molybdenum concentrations above 5 - 6 ppm, and sheep may be poisoned when molybdenum concentrations are greater than 10 - 12 ppm.
- However, the 2:1 ratio is not absolute even in cattle because increasing the copper concentration of the diet even 5 ppm above normal to 13 - 16 ppm will protect cattle against 150 ppm molybdenum.
- Calves may be poisoned by milk from cows on high molybdenum diets.

Mechanism of Action

- Copper and molybdenum form an *in vivo* complex with a molar ratio of 4:3.
- Molybdenum excretion is enhanced by increasing dietary inorganic sulfate.
- Increases in dietary molybdenum and sulfate increase urinary excretion of copper.
- Copper is an important metal component (often at a catalytic site) in many enzymes including: tyrosinase, lactase, ascorbic acid oxidase, uricase, monoamine oxidase, deltaaminolevalenic acid dehydratase, dopamine-beta-hydroxylase, and cytochrome oxidase. Deficiency of copper may reduce certain enzyme activities. The diminished activity of cytochrome oxidase is a sensitive indicator of copper deficiency.
- Progressive atrophy of the myocardium with replacement by fibrous tissue and resultant sudden deaths, usually after excitement or exercise, has been associated with copper deficiency (falling disease) of cattle. This condition, however, is poorly documented and it remains to be experimentally reproduced. A similar condition is reported in pigs and chickens but not in sheep or horses.
- In copper deficiency of some species, there is a reduction in the activity of a copper containing enzyme, amine oxidase, in the aorta. It is hypothesized that this may result in reduced deamination of lysine in elastin, which may result in less conversion of lysine to desmosine, a cross-linkage group of lysine. In turn, this may result in lessened elasticity of the aorta and other major blood vessels. The tensile strength of the aorta is apparently markedly reduced, and there are spontaneous ruptures of the major blood vessels. The myocardium becomes friable.

- In ruminants, osteoporosis and spontaneous fractures have been documented with excess dietary molybdenum and thus a relative copper deficiency. Bone abnormalities associated with copper deficiency have been reported in rabbits, mice, chicks, dogs, pigs, foals, sheep, and cattle. It has been shown that bone cytochrome oxidase activity was reduced in copper deficient chicks.
- Copper is important in the maintenance and function of myelin, and nerve damage and demyelination are key aspects of "enzootic ataxia" and "sway-back" (usually in lambs).

Signs

- Most Species:
    - Anemia characteristic of an iron deficiency (microcytic, hypochromic). Osteoporosis, spontaneous fractures, beaded ribs.
- Many Species:
    - Anemia.
    - Depressed growth.
    - Bone disorders.
    - Depigmentation of hair.
    - Neonatal ataxia.
    - Impaired reproductive performance.
    - Heart failure.
    - Vascular damage.
    - Gastrointestinal disturbances.
- Cattle:
    - Emaciation.
    - Liquid diarrhea (full of gas bubbles) which may begin 8 - 10 days after being placed on a high molybdenum diet.
    - Swollen genitalia.
    - Anemia.
    - Achromotrichia.
    - Prolonged purgation may result in poor weight gains and even death.
    - Sudden deaths.
    - Rough hair coat.
    - Drop in milk production.
    - Loss of libido and general unthriftiness.
- Sheep:
    - Depigmentation of wool.
    - Abnormal wool growth, loss of crimp and quality of wool, stringy wool and anemia in ewes with "enzootic ataxia" (in Australia).
    - In the United Kingdom, "sway-back" occurs in lambs, whereas ewes are usually normal.
    - Enzootic ataxia and swayback are noted in lambs less than 1 month old. The lambs are severely uncoordinated, ataxic, and usually blind.
    - Death results from starvation, exposure, or pneumonia.

Lesions

- Coarse, stringy, poorly pigmented hair or wool.
- Emaciation.
- Hemosiderosis.
- In prolonged cases, osteoporosis and bone fractures have been reported.
- In lambs with "enzootic ataxia" or "swayback", there is lysis of the white matter of the cerebrum and degeneration of the motor tracts of the spinal cord. The damage in the white matter varies from microscopic foci to massive subcortical destruction. There is often neuronal degeneration and demyelination.

Diagnosis

- Clinical signs and lesions.
- Copper and molybdenum concentrations in feeds and forages.
- Good response to the administration of copper.
- Copper and molybdenum concentrations in tissues.

    - Liver-copper concentrations of less than 10 - 30 ppm on a wet weight basis and molybdenum concentrations of greater than 5 ppm are significant. Normal liver-copper concentrations range from 30 - 140 ppm on a wet-weight basis, and liver molybdenum is normally below 3 - 4 ppm.
- Blood.
    - Whole blood copper concentrations of less than 0.6 ppm and molybdenum concentrations above 0.1 ppm are usually present in molybdenum toxicosis-copper deficiency. Normal blood copper concentrations range from 0.7 - 1.3 ppm, while a normal molybdenum level is around 0.05 ppm.

Treatment

- Providing copper orally or parenterally; good response usually. Use caution with sheep.
- Methods:
    - Copper sulfate added to salt-mineral mixture at 1 - 5% depending on molybdenum levels in the feed.
    - Provide 1 gram of copper sulfate/adult cow. Alternative methods include:
        - 1 oz $CuSO_4$/250 gal of water.
        - 1/2-1 lb of $CuSO_4$ to 100 lb of salt.
        - 100 lb of protein concentrate, 100 lb of salt, and 2.5 lb of $CuSO_4$ (feed at rate of 1/6 lb/hd/day.
    - Copper glycinate SQ at 60 mg for calves and 120 mg for mature cattle. May need to be repeated during a season.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Cause Hemolysis
Arsine (arsenic hydride) gas which may come from charging storage batteries	All species	Minutes to hours	Days often lethal; poisoning is rare	
Stibine (antimony hydride) gas	All species	Minutes to hours	Days often lethal; poisoning is rare	
Phenothiazine	(See Toxicants that Cause Primary Photosensitization)			
Propylene glycol (especially when given IV)	All species	Hours	Days potentially lethal; particularly after a high intravenous dose	
Rattlesnakes and other pit vipers (phospholipase A)	All species	Minutes to hours	Days potentially lethal	
Saponin-containing plants	(Hemolysis is theoretically possible, but not well documented, see Poisonous Plants that Affect Gastrointestinal Tract)			
***Brassica* spp.** (kale, brussels sprouts, rapeseed and forage)	(See Toxicants that Cause Goiter)			
Zinc	(See Toxicants that Affect the Kidneys)			

- Other Oxidant Drugs (Acetanilid and Others)
- Saponin-Containing Plants (See Poisonous Plants that Affect Gastrointestinal Tract)
- *Brassica* spp. (See Goitrogenic Toxicants)
- Kale, Brussel Sprouts, Rapeseed, and Forage (*Brassica*)
- Rattlesnakes and Other Pit Vipers (Phospholipase A)

Section XX: Coagulation of Blood and the Function of Vitamin K

Toxicants that Interfere with the Function of Vitamin K

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1. Toxicants that Interfere with the Function of Vitamin K

Coagulation of Blood and the Function of Vitamin K

The circulatory system is a very dynamic tissue, which is in a continual state of repair and regeneration. The hemorrhage that occurs as a result of either normal activities or from various insults (trauma, infectious processes, shock, stress, malignancy, etc.) is arrested through an ordered interaction involving 3 major events.

The **first** phase is comprised of the platelet adhesion reaction in which activated platelets become sticky, attach to exposed endothelial connective tissue elements and build by aggregation to form a platelet plug. In the **second** phase, the so-called platelet release reaction, vasoactive and coagulation-triggering substances are released. The damaged vessel retracts, and the **third** phase, the coagulation mechanism by which soluble fibrinogen is converted to insoluble polymerized fibrin, is triggered.

This discussion addresses only those components of the coagulation mechanism (active in the second to third phases) whose concentration in plasma is influenced by vitamin K and only those compounds which act as vitamin K antagonists.

When the coagulation mechanism is set into motion, 2 separate "pathways" are simultaneously set into operation to effect hemostasis. The "intrinsic route" refers to a relatively slow process (lasting 5 - 15 minutes, *in vitro*), while the "extrinsic route" is a relatively rapid one (lasting 10 - 12 seconds), following contact between blood and damaged tissue. Following activation, both routes operate independently and eventually converge at the "common pathway." At this convergence, a single route (common coagulation pathway) is followed which eventually causes the soluble plasma protein, fibrinogen, to be converted into the insoluble fibrin (see Circulation diagram below).

Within each independent (intrinsic, extrinsic) pathway and in the common pathway, at least one coagulation (clotting) factor that depends on the action of vitamin K for its synthesis is involved. When vitamin K is deficient or inhibited, the flow of the cascade is interrupted, preventing eventual formation of the insoluble fibrin polymer.

The vitamin K-dependent clotting factors include factor VII (in the extrinsic pathway), factor IX (in the intrinsic pathway), and factors X and II (prothrombin) (in the common pathway). These clotting factors are synthesized in the liver and vitamin K is an essential cofactor allowing the carboxylation of the acarboxy coagulation proteins to their functional form. Vitamin K metabolism is tightly conserved in the liver.

A very important enzyme, vitamin K epoxide reductase, is essential for the continued synthesis of new factors VII, IX, X and prothrombin. The action of dicumarol and the anticoagulant warfarin (as well as all other anticoagulant rodenticides) is to tie up this enzyme, preventing recycling of the vitamin K and depleting the liver of the active, reduced form of vitamin K (see Hepatocyte diagram below). When this occurs, final carboxylation (activation of) factors VII, IX, X, or prothrombin ceases. However, factors VII, IX, X, or prothrombin already in the bloodstream (synthesized previous to the anticoagulant insult) are not affected and can participate in the normal clotting mechanism. It is when these still-viable, vitamin K-dependent clotting factors reach the end of their life span that unchecked hemorrhage begins to take place. This is the reason for the usual 5-day "lag" time between ingestion of a toxic dose of an anticoagulant and appearance of clinical signs. Factor VII has the shortest half-life (6.2 hours), and thus it and the extrinsic pathway are the first to shut down. When this occurs, hemostasis is impaired slightly, and a mild degree of hemorrhage may occur, but clinical signs are usually not apparent, because the other pathway (intrinsic) is still operational and serves as a sort of "back-up." During this period of time, laboratory evaluation of the blood will reveal an abnormality in the now defunct (extrinsic) pathway. This abnormality is in the form of an **elevated prothrombin time (PT).**

Once the lifespan of factor IX (in the back-up intrinsic path) is at an end (half-life 13.9 hours), that pathway will be shut down and be defunct. It is at this point that hemorrhage begins to go unchecked and the most common time that the first signs of observable clinical abnormalities are noted. It is also at this point that laboratory evaluation of the blood will reveal an elevated partial thromboplastin time (PTT or APTT) as representative of a defect within that particular (intrinsic) pathway. PT is still elevated. From this point, deterioration of the patient due to hemorrhage may be quite rapid (assuming that no more active vitamin K is added to the system).

Figure 1. Circulation

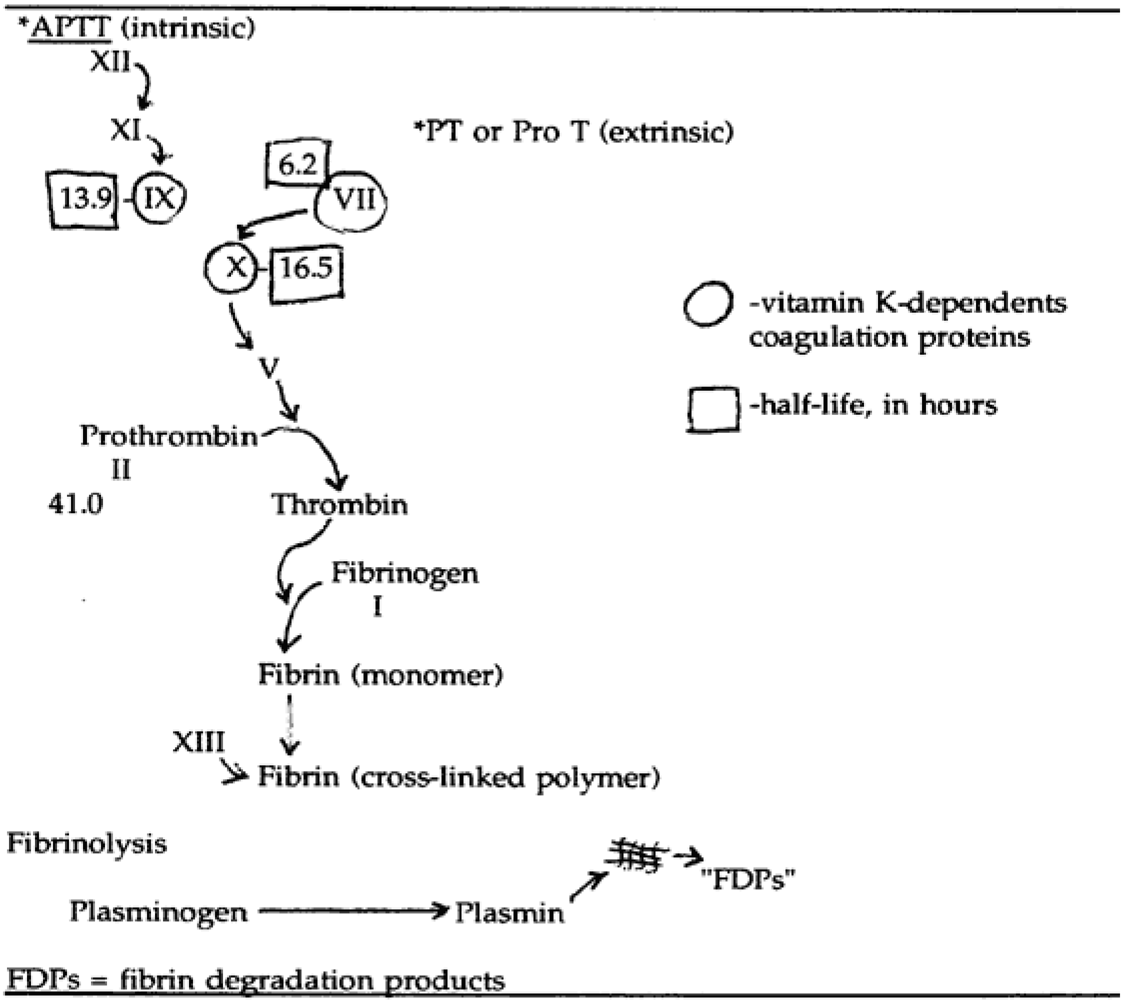
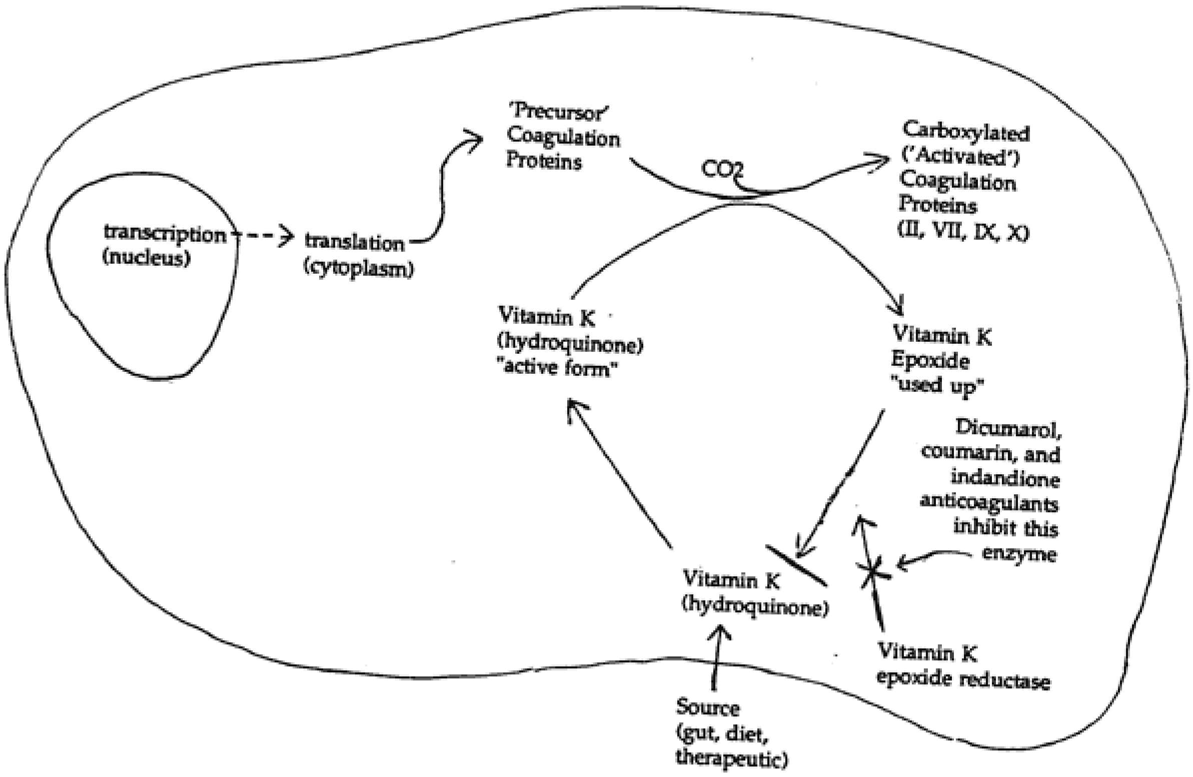


Figure 2. Hepatocyte



Damaged or Moldy Sweet Clover Hay

Melilotus alba - White sweet clover
Melilotus occidentalis - Yellow sweet clover
Melilotus indica - King Island Melilot

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Interfere with the Function of Vitamin K
Cattle	Weeks to months	Days to weeks; often lethal	

Family -
Leguminosae (pulse or bean family)

Description

Melilotus spp.

- Plant: Annual or biennial, upright, branched herb, fragrant odor (similar to vanilla): 3 - 9 feet tall.
- Leaves: Alternate, pinnate, trifoliate, obvate, serrated along the entire margin: 1/2 - 1 inch long.
- Flowers: Small white/yellow, fragrant, appear in numerous slender clusters that arise from the axils of the leaves.
- Fruit: Ovoid, smooth pods contain 1 - 4 seeds.

Sources

Imported from Europe and Asia for hay or use as a cover crop and soil improver. Grows readily throughout the central and northern United States and southern Canada.

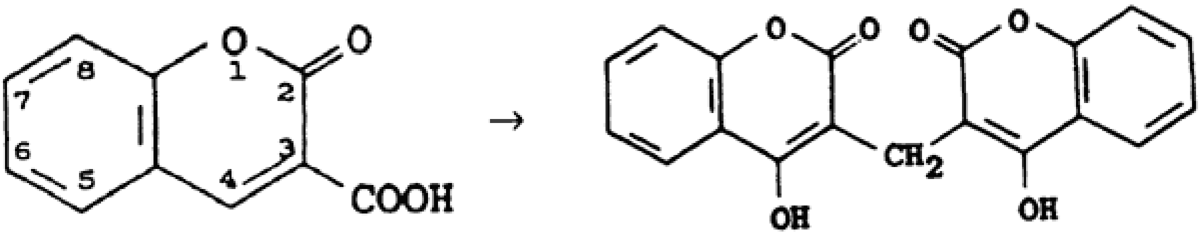
Toxic Principle

Dicumarol, also called bishydroxycoumarin.

Toxicity

- Except for problems related to the formation of dicumarol, sweet clover hay compares favorably to alfalfa hay in quality, utility, and economics. Despite the potential for toxicosis, sweet clover hay has been in rather widespread use since the early 1900s.
- As a result, losses occur annually in Ohio, Indiana, Illinois, Wisconsin, the Dakotas, Nebraska, and other states.
- Formation of dicumarol results from the dimerization and oxidation of the nontoxic compound coumarin, a natural component of the plant which imparts the characteristic fragrance and bitter taste. The conversion process takes place when the clover plant is cut and baled during conditions of high moisture and mild conditions. Various fungi take advantage of the optimum environmental conditions of the hay and metabolize coumarin to dicumarol. Silage may also be affected.

Dimerization - induced by various causes of damage including bad weather, improper curing methods and especially fungi: *Penicillium* spp., *Hemicolor* spp., *Mucor* spp., *Aspergillus* spp.



Coumarin (nontoxic) **Dicumarol** (3,3' methylenebis 4hydroxy coumarin) (toxic)

- The time period required to exhibit observable clinical signs in healthy cattle fed on contaminated hay or silage is dependent on the dicumarol concentrations in the hay. In toxicity trials conducted on 500 - 600 lb steers, no clinical signs were observed after 100 days of feeding hay containing 10 - 20 ppm dicumarol.
- At 30 ppm clinical signs were noted at 132 - 139 days.
- At 60 - 70 ppm clinical signs were noted at 17 - 23 days.

Susceptible Species

- Poisoning is restricted almost exclusively to cattle.
- Minor losses have been reported in pigs, horses and sheep, but these species are rarely affected.
- Cattle appear to be most likely to accept badly damaged sweet clover hay.
- Sheep much more resistant than cattle.

Mechanisms of Action

Proposed to interfere with normal blood clotting as a result of reduction of the concentrations of active forms of clotting factors II (prothrombin), VII, IX and X, due to competitive inhibition (competition between vitamin K epoxide and dicumarol) for the enzyme "vitamin K epoxide reductase" which converts inactive (used) vitamin K epoxide back to its active vitamin K form in the body (see previous discussion).

Signs

- The time from the onset of clinical signs to death is variable, from 24 hours to several weeks, and depends on the degree of exposure and condition of the animal prior to exposure.
- Observable clinical signs in subacute (lower dicumarol levels) cases may be confined to blanching or pallor of the mucous membranes and weakness of the animal apparently due to associated anemia.
- Prolonged or nonstop bleeding occurs in affected animals from minor surgical procedures (castration, dehorning), parturition, or wounds.
- Hematomas of variable size (up to several feet in circumference and protruding up to 12 inches) may be noted on any area of the trunk, neck or limbs.

- Swollen areas may "pit" on pressure (chronic cases) or may be fluctuant (acute cases).
- Gas is not present in these lesions.
- The heartbeat may be increased in strength or the pulse may be rapid and weak.
- Body temperature is normal to subnormal (which may aid in distinguishing the syndrome from infectious diseases), and there often is an absence of pain or inflammation in the areas of subcutaneous hematomas.
- Hemorrhage into the eye may cause blindness, and hemorrhage into the nervous tissue may cause various degrees of paresis, paralysis, or death.
- The animal may be lame from hemorrhage in joints or muscles, or it may be ataxic or motionless.
- Blood may be noted in the oral cavity, nostrils, and urogenital orifices as well as in the milk or excreta.
- Hemorrhage into the thoracic cavity, lungs, pericardium, or mediastinum may cause the animal to become dyspneic.
- Abortions have been noted in cattle. Also, newborn, nursing calves may be affected prior to any observance of illness in the dam.
- Migrating parasites have been suspected of precipitating fatal hemorrhages.

Lesions

- Carcass appears extremely "bruised".
- Subcutaneous swellings consist of fluid (serum) or blood in various stages of clotting.
- Hemorrhages, often subcutaneous and intermuscular, vary in size from petechiae to ecchymosis to hematomas. Gross hemorrhages may be found in almost all tissues. A "layer" of blood may be found beneath the scapulae.
- Histologic lesions may include fatty degenerative changes in the liver and nephritis.
- Notable changes in clinical pathology parameters:
  - Low hematocrit; decreased hemoglobin.
  - Prothrombin time (PT) is elevated (earliest onset).
  - Partial thromboplastin time (APTT) is elevated (intermediate onset).
  - Activated clotting time (ACT) is elevated (delayed onset).

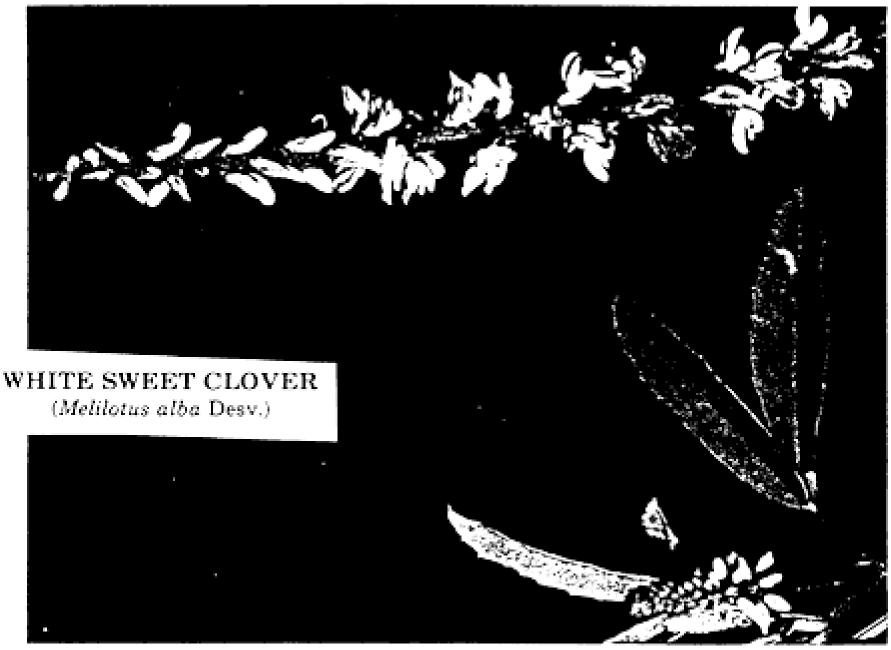
Diagnosis

- History of exposure to sweet clover hay or silage.
- **Note**: Livestock are usually **not** affected by grazing sweet clover pasture.
- Clinical evidence of hemorrhages/hematomas.
- Confirmed by an elevated prothrombin time (PT). **Normal values** may vary between laboratories, but are generally in the range of approximately 20 seconds. Consult local hospitals for assistance in analysis if a veterinary diagnostic laboratory is not available. Special care is required for collection and handling: one part of 3.8% sodium citrate or sodium oxalate is added to a plastic or silicone tube, into which 9 parts of blood (1:9) are collected. Collected blood is kept on ice and centrifuged as soon as possible, preferably within 30 minutes of collection. Plasma is harvested and kept on ice or frozen during transport to the laboratory. To aid in interpretation, it is advisable to collect and submit blood (in the same manner) from a "normal" but unexposed animal (same species) for submission along with the blood of the clinically ill animal(s).
- Analysis of suspect hay or silage for dicumarol content. **Note**: Not all "moldy" sweet clover hay is toxic; conversely, highly toxic hay may have no obvious external manifestations of fungal growth. Stalks, when broken open, may reveal presence of mold growth.

Treatment

- Correction of hypovolemia and clotting factor deficit. If situation is very severe, and if the animal is of sufficient economic or esthetic value, transfusion of fresh whole blood from a donor animal (1 liter per 200 kg of body weight) is used to provide readily available clotting factors and erythrocytes.
- Circumventing the biochemical lesion. **Vitamin K_1** (sold by several companies, e.g. Aquamephyton ® injection, by Merck, Sharpe and Dohme; Veta K_1 ®, by Professional Veterinary Laboratories), at 1 - 3 mg/kg BW. Studies have shown that doses **below** 1 mg/kg are increasingly **ineffective** in reversing the toxicosis. A single dose of 1 mg/kg has been shown to be effective in lowering the prothrombin time to approximately normal levels within 24 hours.
  Note:
  - The smallest needle possible should be used, to prevent hemorrhage at the injection site.

    - The injection should generally be made IM or SQ. Intravenous injection has a greater risk of anaphylaxis.
    - Vitamin K_3 (menadione) has been shown to be **ineffective** as either a preventative or therapeutic measure.
- Remove suspect hay or silage and replace with alfalfa hay (a good dietary source of natural vitamin K). Mild cases of toxicosis tend to resolve without further treatment after withdrawal of the contaminated feed.
- Supportive care (quality feed and ample, fresh water; protection from environmental stresses) is very important. Avoid all unnecessary drugs. Note: All affected animals should be handled with care to prevent exacerbation of the anemic/hypoxic state and to avoid causing additional hemorrhage.
- Correction of organ dysfunction that results from accumulation of extravascular blood (e.g., thoracocentesis) should be attempted **only** if the situation is life-threatening (e.g., severe dyspnea).



WHITE SWEET CLOVER
(*Melilotus alba* Desv.)

Moldy *Lespedeza* Hay

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Interfere with the Function of Vitamin K
Ruminants	Weeks to months	Days to weeks; often lethal	

Sources

- *Lespedeza stipulacea*, Korean *Lespedeza*.
- Sometimes grown in the midwestern USA.

Toxicosis

- Produces a hemorrhagic syndrome in ruminants, very similar to dicumarol toxicosis (moldy *Melilotus*).
- Rarely seen, but may be associated with particularly wet years when *Lespedeza* is put up in hay or silage.
- Deaths due to uncontrollable bleeding were seen in Missouri several years ago. Moldy hay was fed to rabbits and the bleeding syndrome was reproduced, indicating that the hay was involved. Toxic principle has not been isolated.
- Prothrombin time (PT) was elevated, suggesting a vitamin K-associated problem.

Sericea Lespedeza (*Lespedeza cuneata* (Dum.-Cours.) G. Don)
Family - Pea (Leguminosae).
Growth Form - Perennial herb.
Stems - Upright, arching, hairy, up to 4 feet long.
Leaves - Alternate, divided into 3 leaflets, the leaflets oblanceolate, cut straight across or slightly notched at the tip, tapering to the base, without teeth, usually silvery-silky on the lower surface, up to 3/4 inch long.
Flower Arrangement - Flowers 1 - 4, from the axils of the leaves.
Flowers - White, with purple veins, up to 1/3 inch long.
Sepals - 5, green, covered with white hairs.
Petals - 5, arranged to form a typical pea-shaped flower.
Stamens - 10.
Pistils - Ovary superior.
Fruits - Pod finely hairy, 1/4 inch long, 1-seeded.
Habitat - Open areas, particularly in fields and along roads where it is often planted for erosion control.
Range - Mostly in the southern half of the state.
Time of Flowering - September and October.

Anticoagulant Rodenticides

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Interfere with the Function of Vitamin K
Coumarin and indandione anticoagulant rodenticides and pharmaceuticals	Most species	2 days to a week	Days to 6 weeks; often lethal	

Introduction

- In North Dakota and Canada in the early 1920s, the hemorrhagic syndrome of cattle caused by dicumarol was first associated with consumption of improperly cured or moldy sweet clover (*Melilotus* sp.) hay. Later investigations found the coagulopathy to be a result of conversion of coumarin (a natural compound in *Melilotus*) to dicumarol (3,3 methylenebis-4-hydroxycoumarin) as a result of fungal spoilage during the curing process of the hay. (See Damaged or Moldy Sweet Clover handout).
- Subsequent research provided an analog, warfarin, which was shown in the early 1940s to be a more potent anticoagulant. Warfarin subsequently found therapeutic use for various thrombotic and coronary diseases as well as effective use in rodent control.

- Today's anticoagulants are structurally related to coumarin or a similar prototype compound, indanedione. Other commercial rodenticides, notably compound 1080® (sodium fluoroacetate), zinc phosphide, strychnine, cholecalciferol (vitamin D_3) and bromethalin operate by completely different mechanisms and present separate, specific problems for diagnosis and treatment.

Sources

Anticoagulant rodenticides are used extensively by the lay public and professional exterminators.

"First Generation" Anticoagulant Rodenticides

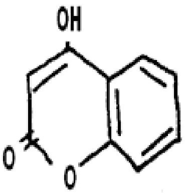
- Warfarin.
  - There are a multitude of commercial warfarin-based anticoagulant rodenticides available for rodent control. These vary widely in concentration and formulations from 0.025% baits (most baits) to 1.0% throw-packs are encountered. Baits are often tan in color and may be mixed with grain. Pharmaceutical preparations (2 - 10 mg tablets) for use in cardiac patients may be a source of accidental exposure to pets from the household medicine cabinet. The chemical name of warfarin is 3(alpha-phenyl-beta-acetylethyl)-4 hydroxycoumarin. All warfarin-containing products should have the "4-hydroxycoumarin" chemical suffix included under the "active ingredient:" on the package label. Some examples of synonyms and brand names: Warf 42®, Coumafene®, Rosex®, D-con® (some types), Warficide®, Prolin®, Ratox®, Raterex®, Banarat®, Coumadin® (pharmaceutical). Prolin® and Banarat® contain sulfaquinoxaline to inhibit synthesis of vitamin K by the bacterial flora of the small intestine.
- Indanediones.
  - Indanedione-containing anticoagulant rodenticides also vary in concentration between products and formulations. Products range from 0.025% bait to 5.0% powder. Pharmaceutical preparations include tablets containing up to 50 mg active ingredient. Indanedione-containing products should contain the chemical suffix "1,3'indanedione" or "1,3(2H)-dione" listed under "active ingredient:". Examples of generic names include: pindone, chlorphacinone, valone, anisindone (pharmaceutical), phenindione (pharmaceutical) and difethialone (pharmaceutical and rodenticide). Brand names include: Chemrat®, Drat®, Rozol®, Ramik®, Isoval®, Diadilan® (pharmaceutical) and D-Cease.

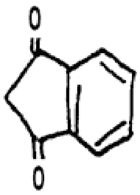
"Second Generation" Anticoagulant Rodenticides

- This group of anticoagulants was developed in the 1970s to answer the problems that existed with the use of the older, first generation anticoagulants. The basic coumarin or indanedione nucleus was retained to give the anticoagulant properties, but chemical structures were selected for increased potency (single lethal feeding potential), and efficacy against resistant rodents. These include the coumarin-based generics brodifacoum, difenacoum, and bromadiolone, and the indanedione diphacinone (sometimes called diphinadione). These are among the most widely used and most toxic anticoagulants. The baits are often blue-green in color. The chemical suffix names of the coumarin types are not consistent, but some of the more common ones can be identified as "benzopyran-2-one" or "1-propanol-1". There are several pharmaceutical preparations available.
- Brodifacoum-containing rodenticides (as of April, 1985) include:

  *Talon®, Enforcer®, *Talon-G®, *Talon Weather-Blok®, De-Mize®, Rodend®, *Weather Blok Bait®, *Havoc®, Bolt Rodenticide®, Ropax®, *D-con Mouse Prufe II®.

- All of today's anticoagulant rodenticides have in common the basic coumarin or the structurally similar indanedione nuclei.





4-Hydroxycoumarin Indane-1, 3-dione

Toxicity and Susceptible Species

- The anticoagulant rodenticides are a potential hazard for all mammals, birds, and possibly other species. The susceptibility varies among animal species and the toxicity of the compounds also varies. Dogs and cats are most frequently involved, with occasional problems encountered in swine, ruminants, horses, pet birds, rodents and rabbits.
- Secondary toxicity.
    - Although consumption of warfarin-poisoned rodents or birds by carnivores does not appear to present a likely hazard for the predator, consumption of tissues from diphacinone-poisoned animals has caused secondary poisoning in eagles, rats, dogs, and mink. Secondary toxicity may rarely occur with other second-generation anticoagulants.

Table 1
Values for Warfarin Toxicity

Species	**Toxic Level Single Dose**	**Toxic Level Repeated Doses**
Rats	50 - 100 mg/kg	1 mg/kg x 5 days
Dogs	5 - 50 mg/kg	5 mg/kg x 5 - 15 days
Cats	5 - 50 mg/kg	1 mg/kg x 5 days
Swine*	3 mg/kg	0.05 mg/kg x 7 days
Ruminants		200 mg/kg x 12 days
Poultry	50% of BW of feed containing 0.1 mg/kg	

*Note that swine are particularly sensitive.

Table 2
Toxicity Values for Various Indanediones

	Single Oral LD_{50}							
Generic	**Rat**	**Mouse**	**Dog**	**Cat**	**Pig**	**Rabbit**	**Duck**	**Human**
Diphacinone	1.5	340	3	15	150	35		5 (LD_{LO})
Chlorphacinone	2.1	1				50	100	
Pindone	280		5 (LD_{LO})			150		50 (LD_{LO})

Table 3
Values for Brodifacoum Toxicity*

Species	**LD_{50} (mg/kg)**	**Species**	**LD_{50} (mg/kg)**
Dog	0.25 - 3.6	Guinea pig	2.8
Cat	25	Rat, Mouse	0.27 - 0.50
Sheep	25 - 33	Mink	9.2
Pig	0.5 - 2.0	Mallard duck	2.7 - 4.6
Rabbit	0.2 - 0.29	Harrier hawk	10

*ICI Americas, 1983.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorption of warfarin is rather complete but occurs slowly, with peak plasma levels seen after 6 - 12 hours. Most of the warfarin is bound to plasma protein, but high concentrations are also found in the liver, spleen, and kidney.
- Metabolism of the coumarins occurs in the liver and involves mixed function oxidase enzymes. Inactive hydroxylated metabolites have been found in the urine. The acute toxicity of the coumarins is reduced when phenobarbital has been given to induce the hepatic enzymes. Vitamin K does not appear to enhance the rate of disappearance of the anticoagulant.
- The anticoagulant rodenticides are eliminated at various rates, depending on the compound and the amount ingested. The compound may accumulate with time, as in the case of an animal ingesting small amounts over several days. The half-life of warfarin in dog plasma is 14.5 hours. The half-life of diphacinone is 15 - 20 days in humans, which compares to a mean of 48 hours for warfarin in humans. The half-life of brodifacoum is yet to be reliably determined, but it is assumed to be at least as bioaccumulative and persistent as diphacinone. These differences in residual half-lives have very important implications when considering treatment of poisoned animals.

Predisposing Factors

- Animals may be of increased susceptibility due to various factors such as: **1**) a high dietary fat intake [fatty acids displace the plasma protein bound anticoagulant increasing the free (active) fraction in the plasma so that more reaches the liver]; **2**) prolonged oral antibiotic therapy (decreased synthesis of vitamin K by intestinal bacteria); **3**) biliary obstruction and liver disease which presumably reduces metabolism and excretion of the anticoagulant and reduces clotting factor synthesizing ability.
- Plasma proteins (albumin) play a significant role in the patient's response to an anticoagulant. Warfarin is over 90% bound in canine plasma. The plasma proteins therefore constitute a great reservoir for warfarin. Warfarin cannot be excreted as long as it is in the tissues or bound to plasma proteins.
- Like fatty acids, certain drugs displace warfarin from the albumin and shunt it down a concentration gradient into the tissue (liver), unless the tissue is already equilibrated, then the warfarin will be free to be excreted in the urine. Drugs known to displace warfarin from albumin in the blood, include oxyphenbutazone, phenylbutazone (also decreases platelet integrity), diphenylhydantoin, sulfonamides, and adrenocorticosteroids.
- Uremia also causes decreased binding of the anticoagulant to serum proteins and may slow excretion of the unbound fraction.
- Aspirin interferes with platelet function. Other drugs generally contraindicated include promazine-type tranquilizers, local anesthetics, nitrofurans, antihistamines, anabolic steroids and epinephrine.
- Although evidence is very limited, there is some reason for concern regarding transmission of anticoagulants to young, perhaps via the milk. Because neonates tend to be hypoprothrombinemic, they may be particularly susceptible to anticoagulant exposure.

Mechanism of Action

- Interference with normal blood clotting as a result of reduced concentrations of clotting factors II (prothrombin), VII, IX, and X, due to competitive inhibition of the enzyme vitamin K epoxide-reductase. (See the section on Coagulation of Blood and the Function of Vitamin K.)
- There does not appear to be any direct hepatotoxic damage from warfarin. Hypoxia and anemia, however, can lead to hepatic necrosis.

Signs

- Although signs have been observed within 1 day of ingestion, there is usually a lag period of 3 - 5 days between exposure and appearance of clinical signs.
- Onset of death may be acute, without the presence of other clinical signs. This is most common when hemorrhage occurs in the cerebral vasculature, abdominal cavity, pericardial sac, mediastinum, or thorax. Outward signs of hemorrhage may not exist in these instances.
- More often, the animal may be initially only depressed, anorexic, and anemic. Pale mucous membranes, dyspnea (due to hypoxia or pulmonary hemorrhage), hematemesis, epistaxis, and bloody or "tarry" feces are common soon thereafter. The animal may be febrile and display nonlocalized abdominal pain. Scleral, intraocular, conjunctival, nasal, oral, urogenital, and subcutaneous hemorrhage may be noted.
- Staggering or ataxia can be observed with severe blood loss.
- The heart rate may be irregular, and the pulse weak.

- Extensive external hematomata may occur at pressure points or traumatized areas.
- Swollen, tender joints are common, especially in pigs.
- Abortions have been noted in cattle.
- Animals experiencing prolonged toxicosis may be icteric from breakdown of impounded blood.

Lesions

- Generalized hemorrhage, especially in the thoracic or abdominal cavities, mediastinal space, periarticular space, periarticular tissues, subcutaneous tissues, and subdural space. There may also be hemorrhage in the gut.
- The heart is often flaccid and hemorrhagic.
- Centrilobular hepatic necrosis may result from anemia and hypoxia.

Diagnosis

- History is very important. Question the owner.
- Clinical signs may vary, but there should be an indication of hemorrhage or swellings.
- Examine the patient carefully.
- Laboratory evaluation of clotting parameters:
    - An elevated prothrombin time (PT) shows up first (24 - 48 hours postingestion) due to the involvement of factor VII (which has the shortest half-life [6.2 hr] of the K-dependent clotting factors [II, VII, IX, and X]). This is followed soon thereafter by an elevated activated partial thromboplastin time (APTT). Platelet count will generally be in the normal to low-normal range.
    - Consult your local hospital if you need help. Send in a citrated blood sample (bright blue stopper) from a "normal" dog to help with the interpretation.
    - Clotting parameter times are suggestive if prolonged beyond 25% of the normal value.
- Chemical detection of specific anticoagulants in biological fluids, vomitus, or baits.
    - Antemortem or postmortem sample of choice is whole blood (refrigerate).
    - Another postmortem sample of choice is liver. Specimens should be wrapped in foil, well identified, sealed in plastic, and frozen during storage and shipment.

Treatment

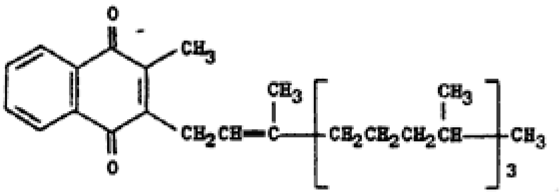
- Patient is presented with clinical complications:
    - Correct low PCV and/or hypovolemia and provide clotting factors as needed using transfusion of fresh whole blood.
    - Handle affected animals with care; sedate (promazine contraindicated) if necessary.
        - 10 - 20 ml of fresh, whole blood/kg BW, IV; first 25% of the dose relatively fast, and the rest by slow drip.
    - Vitamin K_1 (phytonadione, phylloquinone) is the most effective form of the various forms of the vitamin. It is similar to the natural form of the vitamin and works rapidly (begins to reverse the situation in about 30 minutes provided the animal is not anemic and/or hypoxic). Oral vitamin K is faster acting and more effective than the parenteral form. It is absorbed from the GI tract and transported directly to the liver via the portal vein. It should be given with food to enhance its absorption. Use the oral form unless contraindicated (e.g., concurrent administration of activated charcoal, GI hemorrhage, severe depression, etc.). When the injectable form is required use the smallest possible needle and carefully wrap the leg to prevent hemorrhage.
        - Dogs: 3 - 5 mg/kg (lower dose in larger animals), SQ or IM. IV administration may cause anaphylaxis; if you use the IV route, be sure the product is approved for this route and administer over 20 minutes with continuous monitoring; dose may be divided into 2 daily doses if preferred.
        - Cats: 15 - 25 mg, total dose, SQ or IM.
    - Recommended oral doses of vitamin K for dogs and cats range from 0.25 - 2.5 mg/kg/day for warfarin toxicosis and 2.5 - 5 mg/kg/day for long-acting rodenticide toxicosis.
        - Pigs: 2 - 5 mg/kg (lower dose in larger animals), SQ/IM.
          Note - Vitamin K_3 (menadione sodium bisulfite), feed-grade, should be added to all swine rations at 20 g/ton of feed as a good preventative management tool because of the common idiopathic, vitamin K-responsive coagulopathy of swine.
        - Horses: Vitamin K_1 at **not over** 2 mg/kg, SQ/IM; use aseptic techniques for injection.
          Note - Do **not** use vitamin K_3 (menadione) in Equidae. Deaths have occurred from use

of injectable menadione at manufacturer's recommended dosages. Mechanism of toxicity is unknown, but acute renal failure is observed.
    - Ruminants: Vitamin K_1 at 0.5 - 1.5 mg/kg, SQ/IM, not more than 10 ml/injection site. Vitamin K_3 is reportedly of little or no value.
- Duration of therapy.
  - Warfarin.
    - Daily administration is recommended for 10 - 14 days, depending on the amount ingested and severity of the symptomatology.
  - Bromadiolone.
    - Daily administration for 21 days.
  - Diphacinone, brodifacoum (and others).
    - Suggested daily administration for 30 days.
    - Follow in 5 - 7 days after end of treatment period with a prothrombin time (in severe cases, very young, or debilitated patients, continued vitamin K therapy may sometimes be necessary).
  - Pasture and green forages provide some vitamin K and may lessen the need somewhat for prolonged treatment of anticoagulant-exposed herbivores.

    Note: If patient is symptomatic at presentation, it is usually advisable to use a whole blood transfusion and vitamin K_1 injectable, the latter, for the first 1 or 2 days of treatment, or until stable.

  - If dyspnea continues, a thoracic radiograph may be indicated. Thoracentesis to remove extravasated blood may be indicated to save the patient's life, but extreme caution must be exercised to prevent further hemorrhage.
    - Oxygen may be beneficial in severely dyspneic animals.
  - Keep patient warm and still until stabilized. Minimal rates of balanced electrolyte solutions may be used if needed for extra fluids and only after sufficient clotting factors (generally whole blood) are on board.
    - Once stable, the patient can be sent home and dosed with oral form of vitamin K_1. Client education is very important to ensure that the medication is continued as directed.
    - Avoid elective surgery.
    - Avoid protein bound drugs as much as possible.
    - Contraindicated drugs during recovery period include corticosteroids, sulfa drugs, antihistamines, phenylbutazone, epinephrine, aspirin, others (see the section "Predisposing Factors").
  - Owner take-home instructions:
    - No large volumes of fatty foods (table scraps, etc.).
    - Restrict exercise for duration of therapy.
    - Strict attention to daily medication, even if patient looks and acts normal. Clinical relapses have occurred with premature withdrawal of medication.
  - Patient is presented asymptomatic within several hours of a suspected or confirmed exposure:
    - Induce emesis if within 3 hours of ingestion with apomorphine (dog), syrup of ipecac, or xylazine (cat), or 3% H_2O_2 (either species). Do not induce emesis if patient is depressed or recumbent or if other contraindications are present.
    - Activated or superactivated charcoal.
    - Osmotic cathartic (sorbitol). Alternatively, a saline cathartic may be administered after being mixed with at least 5 times as much water. Administer via stomach tube or orally. Effective for as long as bait is in the gut.
    - Decision to begin vitamin K therapy will depend on the situation, i.e., amount ingested, effectiveness of emesis procedure, time since ingestion. In cases of suspected low dose exposures (i.e., < 1/8 of the LD_{50}), may elect (after emetic and activated charcoal, etc.) to give an injection of vitamin K_1, and send patient home with instructions to observe the animal closely for 10 - 30 days, depending upon the compound involved.
      - Vitamin K_3 has the disadvantage of not being as effective as vitamin K_1. Do **not** use vitamin K_3 alone in symptomatic or highly exposed small animals: use vitamin K_1.
    - Adverse effects related to vitamin K_1 therapy generally stem from IV administration. Anaphylactoid reactions occur quite often, including cutaneous manifestations such as

urticaria. Large doses (10 mg/kg) of vitamin K_1 have been associated with Heinz body anemia and hemolysis.



Vitamin K_1

Prevention

Client and pest control operator education.

Differential Diagnosis

- Poor response to vitamin K_1 therapy is helpful in ruling out anticoagulant toxicosis, provided that the animal is not anemic or in liver failure in addition to being poisoned by an anticoagulant.
- Autoimmune thrombocytopenia (AITP):
  - Initial presentation: petechial to ecchymotic hemorrhages on mucous membranes, sclera, skin are characteristic; due to lack of platelets.
  - Platelet numbers will be low (generally below 20,000) unless there is a functional platelet disorder, then numbers may be normal.
  - Otterhound, Foxhound, Basset Hound are predisposed.
- DIC (disseminated intravascular coagulation).
  - Important to identify a primary disease such as neoplasia, pancreatitis, heat stroke, sepsis, chronic active hepatitis, etc. Involves a careful history and physical workup or necropsy.
  - Hematology to confirm: AT III, fibrinogen, plasminogen are decreased.
  - Fibrin degradation products (fibrin split products) are present in blood; kits are available to test in clinics.
- Hereditary diseases (not as common).
  - Von Willebrand's disease.
    - Hemorrhage is often less severe than with anticoagulant toxicosis.
    - Deficiency of a key component (von Willebrand factor) of the coagulation factor VIII, which is itself functional. The defect affects platelet function.
    - Analysis for factor VIII-C and factor VIII-RAg.
    - Scottish Terriers and Doberman Pinschers are predisposed.
  - Hemophilia A.
    - Factor VIII deficiency.
    - Irish Setter, French Bulldog, Cairn Terrier, Greyhound, Poodles, others.
    - Intrinsic pathway is defective in coagulation . . elevated APTT.
- Liver disease.
  - All coagulation factors except factor VII are synthesized in the liver.
  - Severe liver disease usually occurs before coagulation is significantly disrupted. Liver enzymes may indicate damage or, if chronic, may be normal.
  - Portal hypertension may cause a backup and redistribution of platelets to the spleen, resulting in a deficiency in the circulation.
  - Lack of bile secretion into the gut. Required for absorption of fat-soluble vitamin K. Biliary function tests indicate obstruction.

Idiopathic Coagulopathy in Swine

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Interfere with the Function of Vitamin K
Swine	No etiologic agent known	Days to weeks; often lethal	

- A sporadic but notable problem in swine throughout the U.S.
- Affects young, healthy, fast growing pigs under good management conditions.
- Etiology is not known, but appears to involve a variety of factors (nutritional, mycotic, stress, gut flora changes, others?).
- Condition is a primary coagulopathy; liver is not damaged to any great extent.
- Swine coagulation system appears more susceptible to insult than other species of livestock.
- The coagulopathy is vitamin-K responsive (characterized by decreases in factors II, VII, IX, and X).
- Clinical signs: bleeding from mouth, into body cavities, joint areas, and muscles, and deaths.
- Vitamin K3 in the feed (menadione sodium bisulfate, feed grade) at a dose of 20 grams/ton of feed is effective in preventing and at alleviating the problem. Initially, higher doses suggested such as 100 grams/ton are provided for the first several days.

2. Other Toxicants that Affect Hemostasis

Other Toxicants that Affect Hemostasis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	
Toxicants that Affect the Liver and Secondarily Cause a Coagulopathy				Full Table for Toxicants that Interfere with the Function of Vitamin K
Aflatoxin and many other hepatotoxic agents	See Mycotoxins that Affect the Liver			
Many others				
Toxicants that Harm the Bone Marrow				
Bracken fern Pteridium	See Thiaminase-Containing Plants and Other Substances			
Trichloroethylene-extracted soybean oil meal	-			
Benzene	-			
Lead	See Toxicants with Mixed Effects on the CNS			
Cadmium	See Toxicants that Affect the Kidneys			
Chloramphenicol	-			
Toxicants that may Cause Severe Shock and Either Disseminated Intravascular Coagulation or Other Coagulopathy				
Synthetic and natural estrogens	-			
Lindane in human beings	-			
Garbage Toxicoses	See Toxicants that Cause Shock			
Pit Vipers	See Toxicants that Cause Shock			

Toxicants that Affect the Liver and Secondarily Cause a Coagulopathy

- Aflatoxin (See Mycotoxins that Affect the Liver)
- Many others

Toxicants that Harm the Bone Marrow

- Brackenfern (*Pterydium*) (See Thiaminase-Containing Plants and Other Substances)
- Trichloroethylene-Extracted Soybean Oil Meal
- Benzene (bone marrow effect)
- Lead (See Toxicants with Mixed Effects on the CNS)
- Lindane (in human beings)
- Chloramphenicol (especially in human beings)

Toxicants that may Cause Severe Shock and Either Disseminated Intravascular Coagulation or Other Coagulopathy

- Garbage Toxicoses (See Toxicants that Cause Shock)
- Pit Vipers (See Toxicants that Cause Shock)

Section XXI: Toxicants that Affect the Teeth and Skeletal System

Toxicants that Affect the Teeth and Skeletal System

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Acute and Chronic - Fluoride Toxicosis (Fluorosis)

Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Teeth and Skeletal System
All species	Chronic	Essentially permanent; potentially lethal	

Sources and Prevalence

- Fluorine is a reactive nonmetallic element present in varying amounts in soils, water, air, vegetation, and animal tissues. In nature, it is found in a combined (fluoride) form due to its high reactivity.
  - **Acute Fluorosis.**
    - Hydrogen fluoride.
    - Fluoride in the form of the insecticide, sodium fluorosilicate (also called sodium silicofluoride). Now very rarely available for use as an insecticide on and around cattle, hogs, and sheep.
    - As a swine acaricide (sodium fluoride), also rarely encountered.
    - In vegetation or feeds containing extremely high levels of fluorine, also rare.
    - Other fluoride compounds with widely varying toxic properties are also recognized.
    - Consultation with a toxicologist is suggested for any acute fluoride-related toxicosis.
    - Dialysis with fluoridated water.
  - **Chronic Fluorosis.**
    - Chronic exposure from industrial effluents, fertilizers and mineral supplements is the most common cause of fluoride toxicosis.
    - Industrial areas may contain fluoride in the air as a result of processing of metal ores (steel mills, aluminum smelting plants), or manufacturing of fertilizers and mineral supplements from fluoride-bearing phosphate rock. The fluoride effluent from these industrial sources is carried in the wind and settles on vegetation or into water or feed sources. Herbivores are exposed as a result of ingestion of plants in the contaminated pasture or contaminated feed or water.
    - The seeds or grains of crops do not accumulate fluorides, but the plant portion (stalk, stem, leaves) will accumulate fluoride. Airborne fluoride may just settle on vegetation as a significant source.
    - Use of rock phosphate in the diet of animals (rock often contaminated with naturally occurring fluoride) is another possible source.
    - Ground water and soil normally contain varying amounts of fluoride, and may contribute to a chronic buildup of fluoride in the body.
    - Geothermal waters may be a source of high levels.
    - Volcanic ash may be a source of high fluoride contamination.

Toxicity

- Man and animals normally ingest low concentrations of fluoride throughout their lives. Adverse effects are not known to accompany such ingestion. Low levels of fluoride possibly help strengthen bones and tooth enamel.
- Factors that determine an animal's reaction to fluoride ingestion include: **1**) the amount of fluoride ingested, **2**) the duration and variation in amounts of fluoride intake, **3**) the solubility of fluoride ingested, **4**) the species and age of the animal, **5**) the level of nutrition (malnutrition intensifies toxicosis), **6**) others stressors (simultaneous exposure to other toxic or potentially toxic substances), and **7**) individual biological response.

- NRC (National Research Council) dietary tolerances have been established for fluoride in various livestock and vary between 20 and 200 ppm in the diet, depending on species.

Susceptible Species

All species are potentially susceptible to both acute and chronic toxicosis. In general, dogs are more prone to ingest the fluoride-containing insecticides, while chronic toxicosis is noted most often in herbivores grazing on contaminated pastures. Wild herbivores (deer, elk, moose, antelope, hares) are also susceptible.

Absorption, Distribution, Metabolism and Excretion (ADME)

- NaF is rapidly absorbed from the digestive tract (75 - 90% is absorbed by 90 minutes).
- Fluoride is passively absorbed from the gut into the blood stream, where about half is excreted rapidly in the urine - the rest is stored in calcified tissues (bones and teeth). Normal adult bones contain from 1000 - 1500 ppm fluoride.
- Fluoride is cumulative and potentially toxic as long as constant or increasing amounts are ingested over time, otherwise urinary excretion will tend to maintain body fluoride below toxic levels.

Mechanism of Action

- Acute fluorosis.
  - Depends upon the individual fluoride compound.
  - Suggestions have been made of the possible endogenous synthesis of fluoroacetate or fluorocitrate.
  - However, it is known that fluoride (Fl^-) binds to cations disrupting ionic balance. Fl^- binds to Ca^{++}, Mn^{++}, and Mg^{++}. It also interferes with Na^+/K^+ ATPase.
  - Deaths are due primarily to hyperkalemia and associated conduction changes in the heart, as well to hypocalcemia.
- Mechanisms of action in acute toxicoses include:
  - Direct irritation to mucous membranes and skin especially from hydrogen fluoride.
  - Inhalation of fluorides causes pulmonary edema and bronchial pneumonia.
  - Interference with calcium metabolism intracellularly and lowering of plasma calcium due to formation of insoluble precipitates of fluoride and calcium.
- Chronic fluorosis.
  - Excess fluoride intake affects the teeth when exposure occurs during developmental stages (prior to eruption). Faulty mineralization results when the matrix laid down by damaged ameloblasts and odontoblasts fails to accept minerals normally.
  - Enamel lesions cannot be repaired. Dental lesions of chronic fluorosis are characterized by rapid wear of the teeth, especially when coarse, abrasive feeds are fed. Oxidation of organic material in the teeth involved results in a brown to black discoloration of the teeth.
  - The exact mechanism relating fluoride accumulation to the pathogenesis of bone malformation is not known. It is thought to be related to either inadequate matrix and defective mineralization, or to replacement of hydroxyl radicals in the hydroxyapatite crystal structure by fluoride, resulting in a decrease in crystal lattice dimensions. Skeletal fluorosis results in accelerated bone resorption (osteoporosis) and remodeling with production of exostoses and sclerosis, i.e., general disruption of normal osteogenic activity. Bones that are more active metabolically, such as those used in locomotion, chewing, or breathing, are more affected than are bones that are primarily protective and less active in function. Also, growth areas of bones are more affected than less active areas.

Signs

- Acute fluorosis.
  - Vomiting, diarrhea, evidence of abdominal pain.
  - Loss of sensation with tingling of the extremities.
  - Hypersalivation.
  - Sweating.
  - Convulsions.
  - Pulmonary congestion.

    - Ventricular tachycardia, with ECG abnormalities such as tall peaked T-waves, small or absent P-waves, wide QRS complexes, and prolonged PR intervals.
    - Death.
- Chronic fluorosis.
    - Seen mostly in livestock with signs related to the hard tissues of the body. The condition is insidious and the clinical picture is often confused with chronic debilitating problems such as degenerative arthritis. Osteofluorotic (proliferative osteoporosis) lesions are not primarily associated with articular surfaces. Instead, diaphyseal and metaphyseal areas are often severely affected.
    - Dental lesions are noted only in those animals ingesting toxic amounts of fluoride at the time of permanent teeth development (1 - 5 years of age), after the teeth have erupted.
    - Problems of the long bones caused by fluorosis involve osteoporosis and proliferation of spongy bone along the diaphyses of the long bones (joints are spared). Despite the sparing of the joints, eventually the animals become lame. Thus a classical history of fluorosis in cattle is a dairy herd with animals losing condition, producing a decreasing amount of milk, and exhibiting increasing rates and severity of lameness.

Diagnosis

- Based on exposure history (analyze forage, water), clinical signs, bone and tooth lesions.
- Considering the animals' ages, and recognizing the different times of eruption of incisors, and the premature wear on different teeth, the bovine practitioner can readily determine when the exposure occurred (e.g., before or after the animals were purchased; or before or after a new factory moved into the region upwind from the farm.
- Urine fluoride levels (time dependent).
- Bone specimen analysis for fluoride.
- Feed and water analysis for fluoride (time dependent).

Treatment

- Acute fluorosis.
    - Orally-administered calcium gluconate (IV), aluminum or calcium compounds (or milk) to bind fluoride before absorption.
    - Quinidine has been used experimentally to prevent fluoride-induced hyperkalemia. It blocks K^+ efflux.
    - Dialysis to remove fluoride and potassium.
    - After onset of hyperkalemia, calcium gluconate may be given via the fluids, and dialysis used to remove fluoride and potassium.
- Chronic fluorosis.
    - Aluminum sulfate, aluminum chloride, calcium aluminate, calcium carbonate, defluoridated phosphate have been used successfully to reduce the toxic effects of chronically ingested fluoride.
    - Livestock with dental lesions and the inability to eat sufficient amounts to sustain high productivity often should be culled from the herd.

Prevention

If animals must drink water which is high in fluoride, be sure the roughage in their diet has a low fluoride level.

Miscellaneous Problems Associated with the Bones and Teeth

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Teeth and Skeletal System
Tetracyclines	Esp. young animals	Chronic	Essentially permanent; unlikely to be lethal	
Congenital porphyria (confusion factor)	-			

- Tetracyclines.
  - Incorporated into feed rations (Aureomycin, Terramycin).
  - Adverse effects include nephrotoxicosis and alteration of the intestinal microflora.
  - Tetracyclines also affect bone and tooth metabolism by chelating calcium to render the calcium unavailable.
  - The teeth and bones of animals given tetracyclines during formative stages may be discolored yellow or brown; and enamel dysplasia or bone deformities are possible.
  - *Tetracyclines* also cause softening of the tooth enamel when consumed during the period of tooth development. Failure to recognize this phenomenon and errant prescription of tetracyclines to animals with teeth yet to erupt can result in lawsuits against veterinary practitioners. Although generally not a concern for older animals, chronic dosing might also discolor the teeth (when the enamel is sufficiently transparent that the color can show through).
- Congenital porphyria.
  - A rare genetic condition affecting domestic cats, cattle, and pigs.
  - Cats.
    - Excessive accumulation of brownish pigment in the bones and teeth, due to overproduction of uroporphyrins and coproporphyrins, which cannot be utilized in heme biosynthesis.
    - Cats suffer severe kidney damage, severe anemia and photosensitivity.
  - Cattle, pigs.
    - Porphyrin accumulations due to interference in hemoglobin catabolism.
    - Cattle - Photosensitization of white areas of skin. Dark-colored urine.
    - Pigs - Do not become photosensitized.
    - Teeth, bones and soft tissues of both species are dark pink and fluoresce under ultraviolet light.

Additional Toxicants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)	Full Table for Toxicants that Affect the Teeth and Skeletal System
Enrofloxacin	Young animals	Days to weeks	Essentially permanent; rarely lethal	
Thiram (fungicide)	Poultry (chickens)	Chronic	Permanent (shortened bones); unlikely to be lethal	
Vitamin A	Cats	Chronic	Essentially permanent (cervical spondylosis); potentially lethal	
Cadmium	See Toxicants that Affect the Kidneys			
Molybdenum **toxicoses / copper deficiency**	See Toxicants that Cause Skin Effects Other than Photosensitization			
Iron	See Toxicants that Affect the Liver			
Cyclopiazonic acid (rare)	-			

- Enrofloxacin
- Thiram (fungicide in poultry)
- Cadmium (See Toxicants that Affect the Kidneys)
- Molybdenum Toxicoses/Copper Deficiency (See Toxicants that Cause Skin Effects Other than Photosensitization)
- Congenital Porphyria
- Iron (See Toxicants that Affect the Liver)
- Cyclopiazonic Acid (Rare)

Toxicants that Cause Blindness

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Annotated Table of Toxicants that Cause Blindness
<!--[**Back to Main Chapter**]-->

Specific Agents	
Ivermectin	(See Toxicants that Cause Central Nervous System Depression)
Ammonia (Corneal Damage) in Poultry	(See Inorganic Compounds that Affect the Lungs)
Phenylarsonics	(See Toxicants that Cause Paralysis)
Lead	(See Toxicants with Mixed Effects on the Central Nervous System)
Hexachlorophene	(See Toxicants with Mixed Effects on the Central Nervous System)
Bromethalin	(See Toxicants with Mixed Effects on the Central Nervous System)
Carbon disulfide	(See Toxicants with Mixed Effects on the Central Nervous System)
Methanol in Primates	(See Toxicants that Cause Acidosis)
Water Deprivation/Sodium Ion Toxicosis	(See Toxicants Associated with Central Nervous System Stimulation or Seizures)
Vitamin A (Deficiency or Chronic Toxicosis)	-
Rapeseed (*Brassica*)	(See Toxicants that Cause Goiter)
Cocklebur (*Xanthium*)	(See Poisonous Plants that Affect the Liver)
Buttercup (*Ranunculus*)	(See Plants that Affect the Digestive Tract, Irritant Oils)
Manchineel tree (*Hippomane*)	(See Other Plants that Affect the Skin)
Desert spike (*Oligomeris*)	(See Toxicants that Cause Stimulation or Seizures)
Phenothiazine-Induced Corneal Damage	(See Toxicants that Affect the Skin (Photosensitization))
Other Photosensitizers	(See Hepatogenous Photosensitizers and Toxicants that Cause Skin Damage by Primary Photosensitization; includes *Ammi majus* or *Cymopterus watsonii* fed to poultry - pigmentary retinopathy)
Vacor ® (Pyriminil; banned rodenticide)	(See Toxicants with Mixed Effects on the Central Nervous System

Toxicants that Cause Bloat in Ruminants (Last Updated: 9-Aug-1999)

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Annotated Table of Toxicants that Cause Bloat in Ruminants
<!--[**Back to Main Chapter**]-->

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Alfalfa (*Medicago sativa*)	Ruminants	Hours	Hours to a day; often lethal
Soybean overload (*Glycine max*)	Ruminants	Hours	Hours to a day; may be lethal
Diet changes	Ruminants	Hours to 2 days	Days; often lethal
Sweet crude oil (Hydrocarbons)	(See Toxicants that Affect the Respiratory System)		
Ammonia toxicoses (urea)	(See Toxicants with Mixed Effects on the CNS)		
Bacteria that form insoluble slime	[See Bartley et al. Digestion and Metabolism in the Ruminant. (1975) pp.551-562.]		

Toxicants that Cause Shock

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Annotated Table of Toxicants that Cause Shock
<!--[**Back to Main Chapter**]-->

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Rumen overload	Ruminants	Hours	Days to weeks; often lethal
Garbage	(See Other Mycotoxins, Bacterial Toxins and Zootoxins that Affect the Gastrointestinal Tract)		
Arsenic	(See Toxicants that Affect the Gastrointestinal Tract)		
Some snake bites	(See Toxicants that Affect Peripheral Circulation)		
Iron dextran	(See Toxicants that Affect the Liver)		
Sulfonamides	(See Toxicants that Affect the Kidneys; see also Histamine)		
Polysorbate 80 in dogs (Tween 80®) (Histamine releaser) (drug vehicle)	-		
Numerous biologicals (Anaphylaxis)	-		
Other drugs			

Appendices

Botanical Terms

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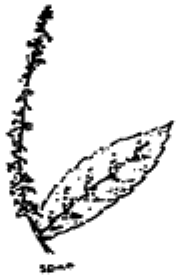
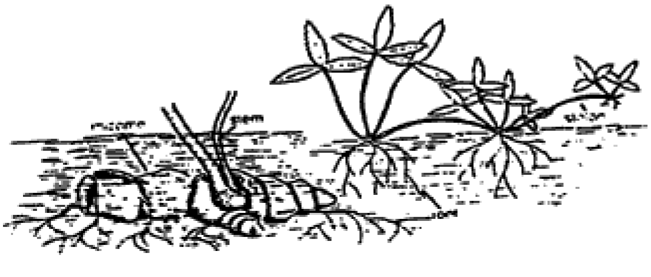
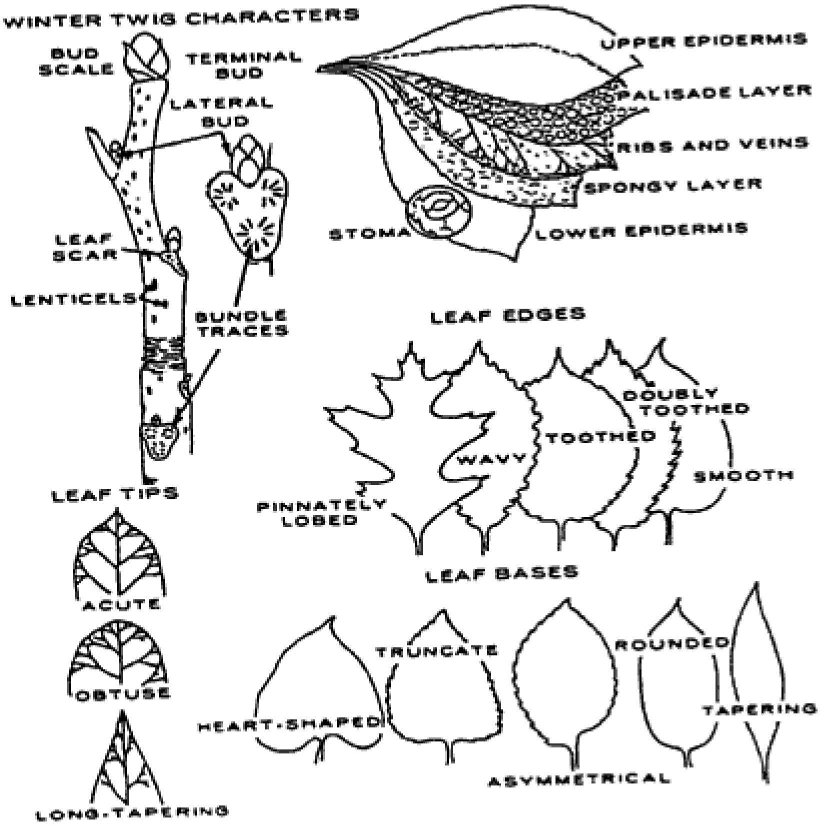
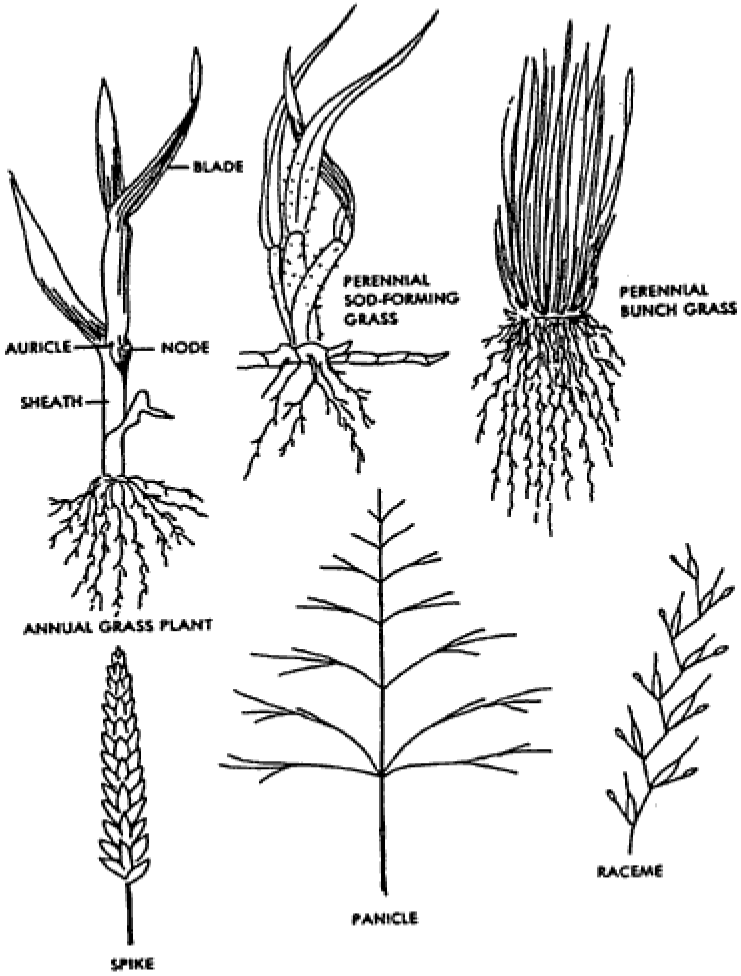
(For Information Purposes Only)

Alternate - One leaf per node, not opposite each other (leaves, etc.).
Annual - Lives only one season.
Axil - The upper angle where the leaf joins the stem.
Bracts - Modified leaves, green or colored, associated with the flower.
Calyx - The outer circle of floral leaves (sepals); usually green, sometimes like petals, may be separate or joined.
Compound - Divided into separate leaflets (leaf).
Corolla - Showy inner floral envelope, composed of petals.
Deciduous - Leaves, fruit, etc., are shed at end of year.
Dioecious - Male and female reproductive organs on separate plants.
Entire - Without lobes or teeth (leaf).
Erect - Single stem.
Glabrous - Smooth, without hairs.
Glaucous - With a waxy whitish coating, shines when rubbed.
Habit - How does it grow, what is it like, e.g., erect, herbaceous, etc.?
Habitat - Where does it grow, what are the best conditions for growth?
Head - A crowded cluster of stalkless flowers.
Herbaceous, herbs - Fleshy, nonwoody plants.
Inflorescence - The flower cluster, how flowers are arranged on stem.
Involucre - A circle of bracts supporting a flower or flower cluster.
Irregular - Not symmetrical (flower).
Linear - Long, narrow, with veins parallel (leaf).
Lobed - Indented, with rounded outer projections (leaf).
Palmate - Divided or lobed to radiate from one point, like the fingers on a hand (leaf).
Panicle - An elongated, compound, branched flower cluster.
Peduncle - Where inflorescence is attached.
Petal - One of the segments of the corolla, may be separate or joined basally, usually colored.
Perennial - First season produces leaves only, second season reproduces with seed production, etc.
Petiole - The leafstalk.
Pinnate - Compound, with several or many leaflets arranged in pairs or alternately along a midrib (leaf).
Pistil - Central female organ of a flower, composed of a swollen ovary at the base; the style which is a slender stalk; and the stigma which is a divided or knobbed tip.
Pubescent - With soft down hairs.
Raceme - A long cluster of flowers arranged singly along a stalk, each flower has its own small stalk.
Rays, ray flowers - The flat straplike blades that encircle the disk flowers (e.g., a daisy).
Rhizomes - The creeping underground stem of plants.
Sepal - A small modified leaf near the rim of the flower.
Spike - A long flower cluster. The stalkless or nearly stalkless flowers are arranged along the stem.
Stamen - The male flower organ, composed of a slender stalk with a knoblike anther, bears pollen.
Stolon - A horizontal branch either above or below ground which produces new plants from buds at its tip, i.e., runner.
Stipule - A small leaf-like appendage at the base of the petiole.
Umbel - An umbrella-like flower cluster with all the flower stalks radiating from the same point.
Utricle - Any of various small pouches or saccate parts of a plant body.
Whorl - Three or more leaves, etc., radiating from a single point.

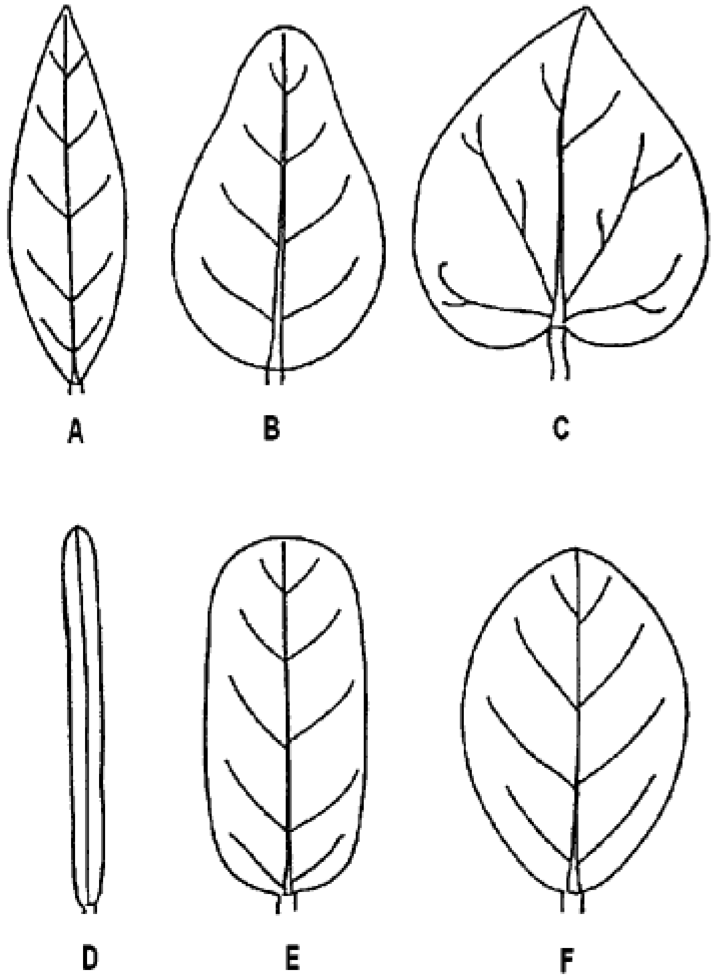



stem

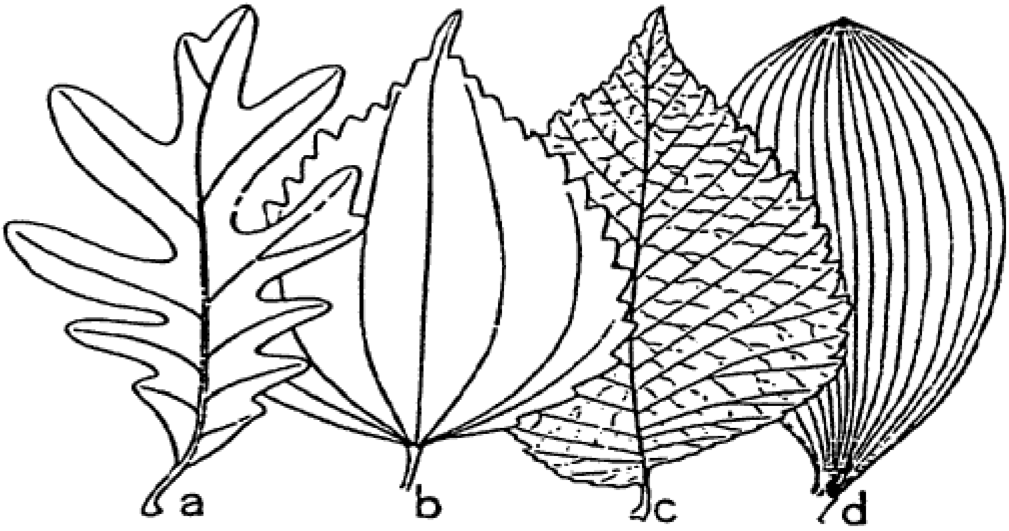

WINTER TWIG CHARACTERS
BUD SCALE
TERMINAL BUD
LATERAL BUD
LEAF SCAR
LENTICELS
BUNDLE TRACES
UPPER EPIDERMIS
PALISADE LAYER
RIBS AND VEINS
SPONGY LAYER
STOMA
LOWER EPIDERMIS
LEAF EDGES
DOUBLY TOOTHED
TOOTHED
WAVY
SMOOTH
PINNATELY LOBED
LEAF TIPS
ACUTE
OBTUSE
LONG-TAPERING
LEAF BASES
TRUNCATE
ROUNDED
HEART-SHAPED
TAPERING
ASYMMETRICAL



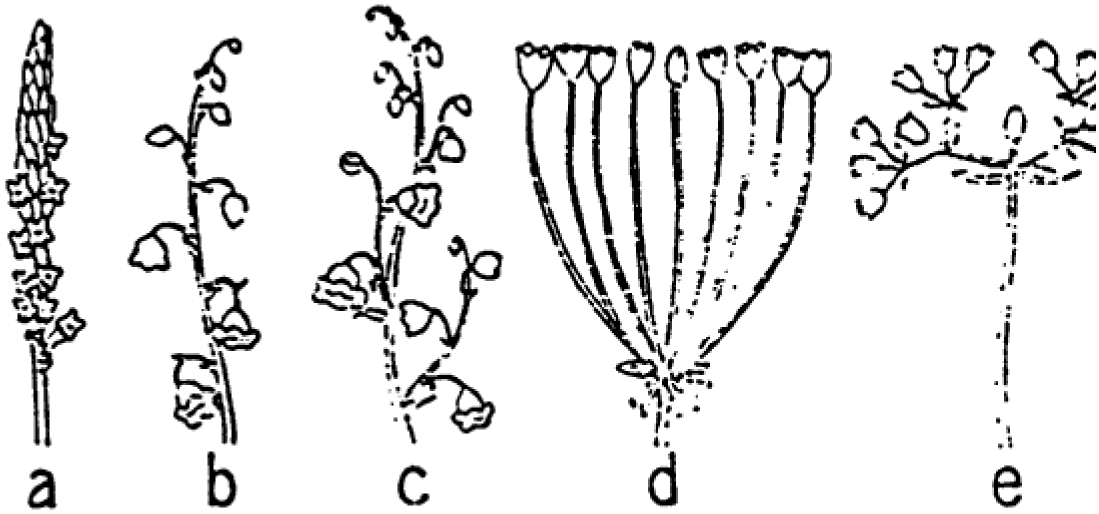
Leaf Arrangements



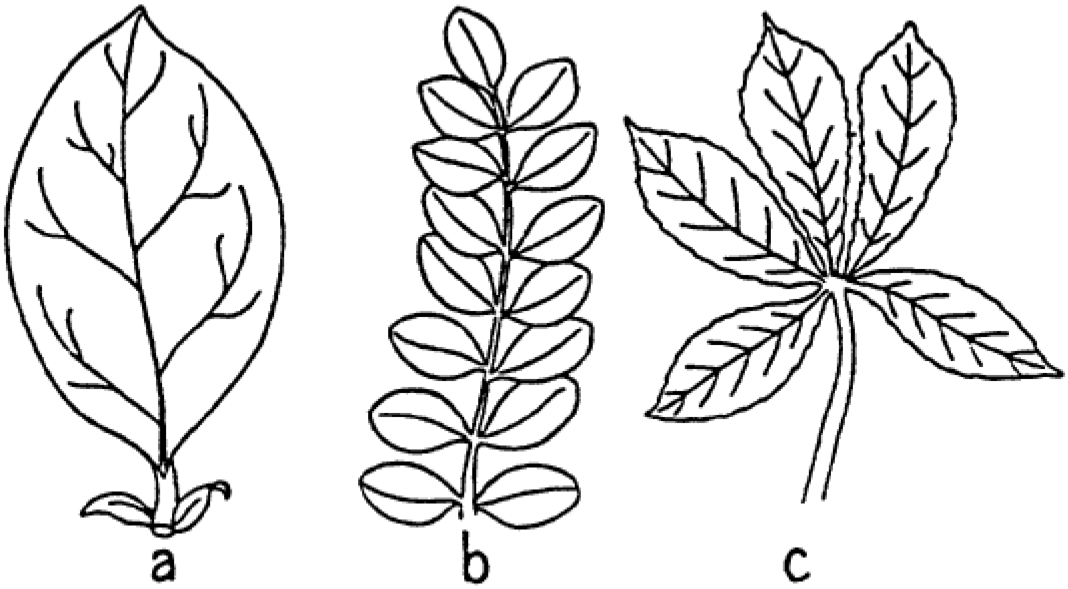
The shape of leaves. **A** - Lanceolate. **B** - Ovate. **C** - Heart - shaped or cordate. **D** - Linear. **E** - Oblong. **F** - Oval.



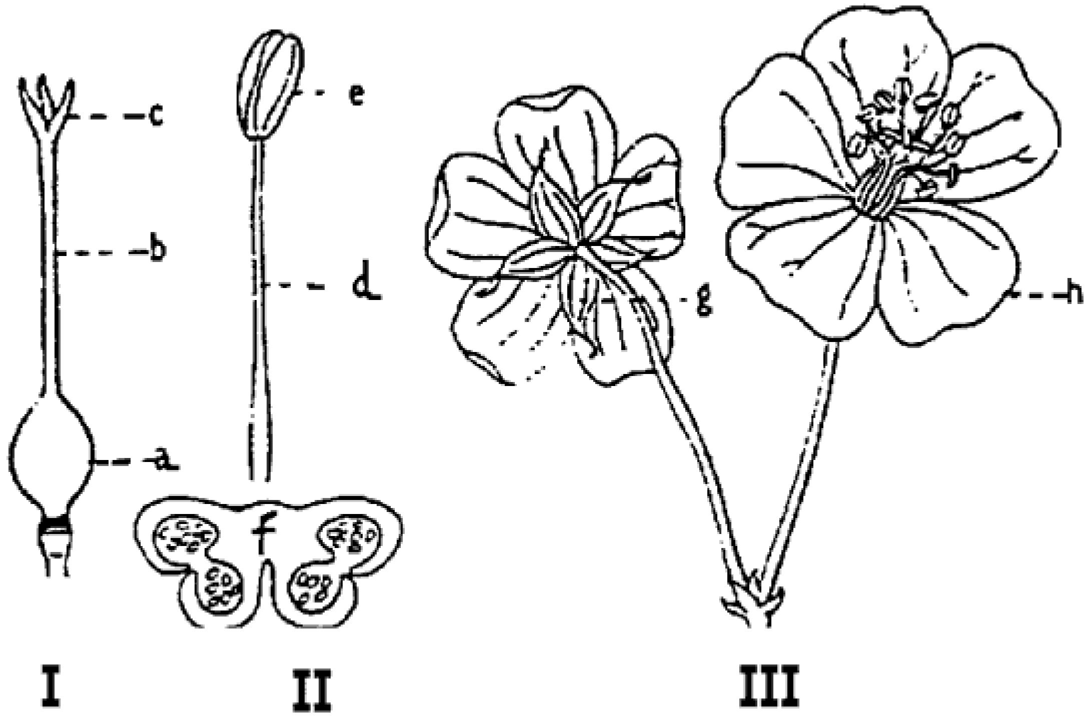
Leaf margins and venation. **a** - Pinnately veined, lobed leaf of oak. **b** - Palmately veined, toothed leaf of nettle. **c** - Netted-veined, doubly toothed leaf of elm. **d** - Parallel-veined, entire leafof false Solomon's seal.



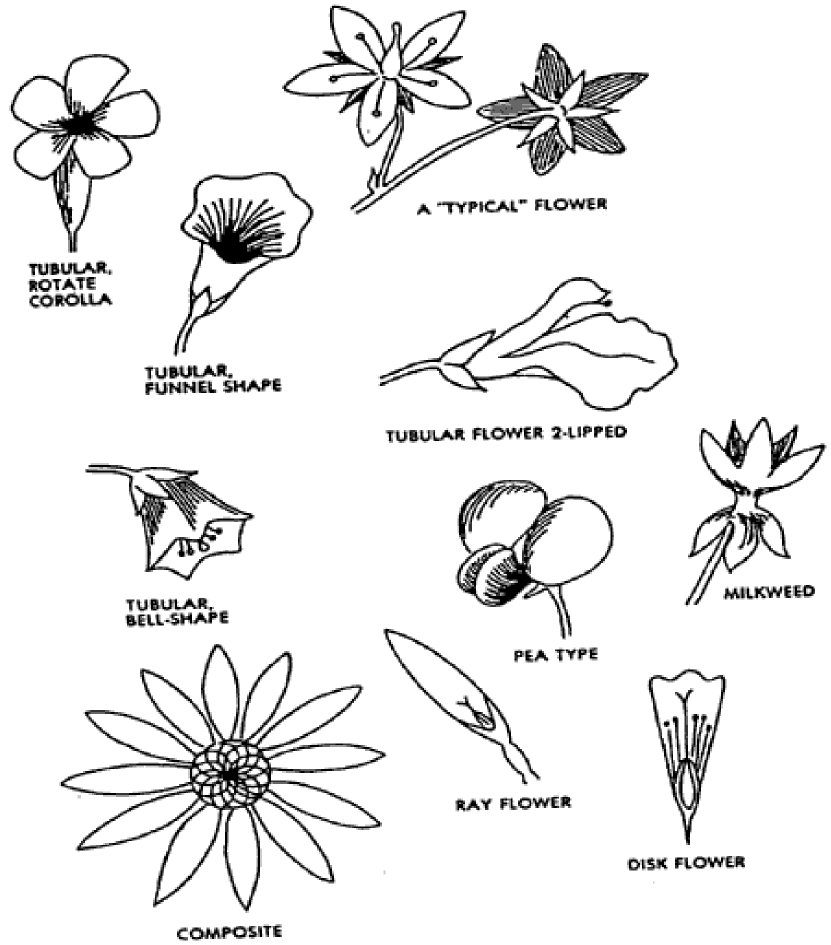
Types of Inflorescence a - Spike. **b** - Raceme. **c** - Panicle. **d** - Umbel. **e** - Cyme.



Complete, Simple and Compound Leaves. a - Simple leaf, complete with stipules. **b** - Pinnately compound leaf. **c** - Palmately compound leaf.



The Complete Flower. I - Pistil, **a** - ovary, **b** - style, **c** - stigma. **II** - Stamen, **d** - filament, **e** - anther, gross view, **f** - anther, cross-section. **III** - Perianth **g** - sepal, **h** - petal.



Flower Characteristics

Absorption, Distribution, Metabolism, and Elimination: Differences Among Species

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Introduction

Why be concerned with species-associated differences in Absorption, Distribution, Metabolism, and Elimination (ADME)?

One reason is that much of vertebrate toxicology and pharmacology is comparative. In general, most of the differences among these species with regard to their susceptibility to negative or positive impacts of various drugs and other toxicants are related to two major factors: **i)** differences in the likelihood and degree of exposure; and **ii)** differences in processes involved in ADME. Much less often, marked differences among the susceptibility of specific receptors explains the variation in effect on vertebrate species.

Safety assessment studies that reliably predict hazards of various drugs and other chemicals to human beings or other species "of concern" can be achieved only through selection of appropriate species for study. Thus, identification of laboratory animal species that absorb, distribute, metabolize, and eliminate xenobiotics in ways similar to those in human beings or the other species "of concern" is essential for rational research on the safe use of toxicants in and around these species.

Currently, much of the activity of industrial toxicologists addresses the question of whether and why human beings are less susceptible to the toxic effects of a given xenobiotic than the more sensitive laboratory animal species. When human beings are demonstrated to be less sensitive than the laboratory animals in which problems have been detected, this usually means less controversy, less regulation, and sometimes, more sales of the xenobiotic under review.

For example: Recent work at the (Chemical Industry Institute of Toxicology (CIIT)) has shown that the air pollutant, 1,3-butadiene, which was listed as hazardous in the Clean Air Amendments, may pose less of a risk of cancer to humans than originally thought. **Mice** were especially sensitive to the carcinogenic effects; while **rats** were 1,000 times less sensitive. In comparative studies of liver metabolism, human beings metabolized 1,3-butadiene in much the same way as rats. This was good news for the manufacturers of 1,3-butadiene.

Similarly, mice hydrolyze 6-propylthiopurine to mercaptopurine which causes potent carcinogenesis; whereas human beings oxidize the drug in two positions without hydrolysis, and the end products are not carcinogens.

Although it is to the advantage of manufacturers to direct attention to the limits of extrapolation (because of species differences) with regard to human safety - it is to their disadvantage to do so with regard to effects on other species in the environment. Typical protocols for the "ecological" effects of toxicants involve assays of direct toxicity to one or two algal species, a vascular plant, a daphnid, a bivalve (sometimes), a fish (or two, usually a cold water [e.g., trout] and warm water [e.g., bluegill] species), and a bird (occasionally two species - most often a mallard and a quail). From these species, regulations are drawn that, in effect, extrapolate to all other life forms in the area exposed to the chemical under development. Generally, safety factors (typically 1:100 to 1:1,000,000 when applied to avoid human health), which allow for ignorance of the potential effects of a chemical as well as individual variation, are minimized with regard to wildlife. Thus, despite the usual absence of knowledge on the direct toxicity or the ADME in a range of exposed non-target species, small or non-existent safety factors are the rule in effluent permitting (point-source contamination) as well as in approval to market chemicals for purposeful outdoor application with anticipated "non-point-source" environmental contamination (e.g. agricultural or lawn pesticides).

A key aspect of pesticide toxicology is selectivity. Unfortunately, target species virtually always co-inhabit places with closely related non-target species. Selective toxicity is exploited to the greatest degree in control of weeds that compete for space and nutrients with crop plants, and in control of pests (including pathogens such as bacteria, protozoa, fungi, helminths, and arthropods) on or in animals, and to a lesser degree in control of unwanted herbivorous and omnivorous birds and rodents, as well as mammalian carnivores. Problems arise when the differences in susceptibility and exposure between the target species and the non-target species are insufficient to protect the latter. In the view of the author, although acute effects of pesticides on ecosystems are highly visible and thus often controlled, *direct subacute and especially indirect toxic effects*, may readily impact ecosystem functioning.

Animal/Environmental Interactions that Predispose to Poisoning (Vary with Species)

- Animals explore the environment in part by tasting what they find.
- When hungry, animals must eat whatever food is available.
- Overgrazing or sudden introduction to a new environment increases the likelihood of ingestion of poisonous plants.
- Co-evolved species tend to be poisoned less often than domestic species.
- Animals often drink from streams, puddles, and wells not suited for humans or animals.
- Animals breathe whatever air is available and are often trapped indoors (and less often outdoors) in toxic gases. Roaming increases likelihood of exposure to other chemicals-potentially resulting in accidental or malicious poisoning.

Maturation and Aging

Differences among species in rates of aging are believed to be attributable to differences in metabolic rates and associated cumulative oxidative injury.
A range of factors may influence ADME (Absorption, Distribution, Metabolism and Excretion) and other aspects of susceptibility to hazards related to a given toxicant. Included among many, these are: Maturity at birth.
Time to sexual maturity.
Life span.

Age-Related Differences in Absorption

Drug absorption in the neonate is influenced by a number of factors that differ from the adult. For example, relative to the adult, the neonate will tend to differ as noted below:

Gastric acid secretion	Low
Gastrointestinal motility	Immature
Gastrointestinal anatomy	Immature
Microbial population	Stomach - high (human) Rumen low
Intestinal enzymate activity	Low
Mucosal absorbing area	Low
Blood perfusion	Variable
Diet	Potential interactions with milk (calcium, protein)

Miscellaneous Factors Related to Maturation and Aging

- Infant BBB is much more permeable than in the adult.
- Several enzymatic processes of metabolism are very low or virtually absent the first few weeks of life.
- Infant has lower glomerular filtration rate.
- Young of some species rely on milk as the major source of nutrition, which may put them at risk of high level exposure to persistent, fat soluble toxicants. Other species may rely on egg yolk, which like milkfat tend to contain considerable concentrations of fat soluble, difficult-to-metabolize toxicants.
- Caloric intake in most domestic species is relatively high - especially in the young of rapidly growing species > pigs, dogs, cattle, horses, etc.
- Old dogs/cats commonly have decreased glomerular filtration rates, reduced metabolic capacity > longer of xenobiotic half-lives.
- Diseases of old age are common in dogs, cats, some horses.
- Diseases of old age are not as often a significant problem in food animals (shipped for slaughter).

Disease-Related Differences

Regardless of the age, disease status may alter organ function, hydration, body temperature, metabolic rate, and other physiologic parameters, and thus may influence ADME and susceptibility to various xenobiotics.

The following are a few examples:

- Parasitism may be a serious problem, and may alter the intestinal or dermal barrier as well as serum protein status, and sometimes the function of the liver, kidneys, lungs or other organs involved in ADME.
- Infectious diseases may be a common or rare factor compromising the patient in various ways depending on the organs involved and the character/severity of the process.
- Preexistent metabolic disorders, glandular disorders, or organ failure are relatively common and can complicate diagnosis and management.

Various Genetic Factors Influence Individual Variation
Interspecific Differences -
Example - Non-steroidal Anti-inflammatory Drugs
Plasma halflife of drugs in four species of experimental mammals. Differences among species are related to pharmacokinetic variations in ADME.

Halflife (hours)				
NSAID	**Rat**	**Dog**	**Monkey**	**Human Being**
Piroxicam	6 (males) 16 (females)	45	5	45
Indomethacin	4	0.3	0.3	2
Naproxen	5	35	1.9	13.9
Ibuprofen	1	2.5	-	3
Phenylbutazone	6	6	7	72
Fenprofen	8	4	0.3	2.5
Sulindac	4	-	-	8

Human beings are predisposed to phenylbutazone toxicosis since the halflife in man averages 3 days as compared to the monkey, dog, horse, rabbit, rat, and guinea pig, which metabolize the drug more readily and have halflives of 3 to 6 hours.

1. Species Differences in Absorption

Dietary Habits of Various Species Groups Diet, as well as the structures and physiologic adaptations that accommodate various diets, affect the material available to bind the toxicant, degree of mastication of the material containing the toxicant, microfloral reactions, acidification, digestion, rate of passage, and rate of absorption.

I. Mammals (>4,000 species)
A. Carnivores - Simple digestive tract for easily digested, nutrient-rich food
  a. Felids (eat viscera of prey)
  b. Vampires
  c. Odontocete and **baleen whales**
  d. Insectivores

Evolutionary strategy of carnivores -
Let the herbivores deal with (avoid, metabolize, and eliminate) plant toxins and mycotoxins on plants - after all, they typically are less toxic than the plants they eat - plus they are nutrient-dense).
Evolutionary liabilities of carnivores -
Don't thrive when there are not enough herbivores to eat. Highly exposed to fat-soluble, slowly metabolized xenobiotics that accumulate via food chains - especially when they rely on long aquatic food chains. Bioaccumulation factors (the ratio between the concentration in animal tissues and that in the environment, e.g., water) can reach many orders of magnitude.

B. Omnivores - More complex digestive tracts: e.g. **swine**, **some rodents**

C. Herbivores - Much more complex - longer transit times, efficient absorption

a. Ruminants

Structure/function is even more age-dependent than in monogastrics

Preruminant vs. ruminant - depends on age and diet - young **calf** or **lamb** is more like a monogastric than a ruminant - until adapted to high roughage diet. This influences ruminal toxification, detoxification, and dilution of toxic agents.

Rumen dilutes and detoxifies many toxicants but toxifies others. For example, the rumen is a highly anaerobic place which tends to reduce a number of compounds (thus converting nitrate to much more toxic nitrite). Rumen is a reducing environment:

Nitrate (NO_3) converted to nitrite (NO_2)
Nitrite then oxidizes hemoglobin (Fe^{++}) to methemoglobin (Fe^{+++})

Dilution of xenobiotics in the rumen is greater than in the stomach of a monogastric and occurs immediately after ingestion.

Binding to fiber (high fiber diets) can significantly reduce bioavailability of some xenobiotics - e.g. some mycotoxins.

Microbes in the rumen metabolize many xenobiotics:

Break epoxides of trichothecenes, which detoxifies these compounds.

Convert non-protein nitrogen sources (NPN e.g. urea, biuret) to ammonia and then ammonia to microbial protein, which is later digested in the abomasum and intestine. The animal is protected from ammonia toxicosis only when the intake of NPN is sufficiently low, the rate of hydrolysis is sufficiently slow, the rate of microbial protein synthesis is sufficiently high.

When the rumen contains excess ammonia, the pH increases (ruminal alkalosis) due in part to conversion of ammonia ($NH3$) to ammonium ions ($NH4^+$). As more ammonia is generated, and fewer protons are available for this reaction, the neutral $NH3$ is absorbed across the rumen and causes clinical signs of toxicosis. Also, the elevated pH causes a lack of rumen motility, which results in acute bloat.

Despite the ruminal alkalosis, the affected animal develops a systemic acidosis and hyperkalemia, which can result in cardiac arrhythmias that terminate in death.

b. Camelids

Similar to ruminants, but forestomachs are configured differently.

c. Posterior fermenters e.g. **horses, guinea pigs, hamsters**

Microbial digestion of plant material by flora in the cecum and especially the colon is essential for the horse. Predisposed to antibiotic-induced entero-colitis.

d. Fruit eaters e.g. **some bats, some primates.**

D. Omnivores

Many **rodents**.
Swine } have some characteristics of posterior fermenters.

II. Birds

Raptors
Fish-eating birds (herons; also some raptors)
Dabbling ducks
Diving ducks
Insectivores
Seed eaters
Nectar-feeding birds (hummingbirds)
Algae/crustacean filter feeders (flamingos)

III. Reptiles

A. Carnivores

Venomous, non-venomous

B. Herbivores

C. Insectivores

IV. Amphibians

Herbivorous as tadpoles (often eat algae); insectivorous/carnivorous as adults

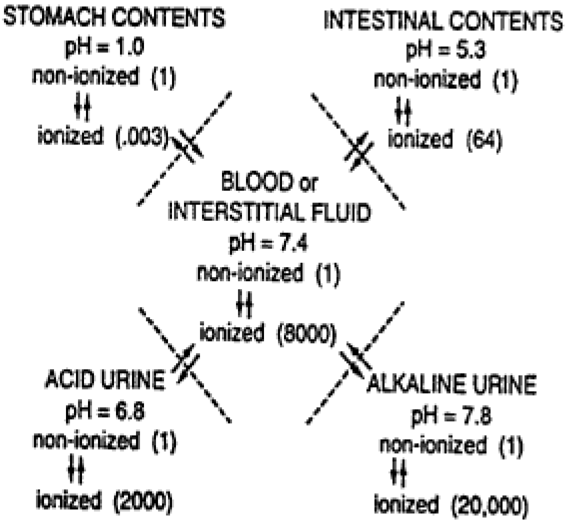
V. Fish

Herbivores, carnivores

Differences in pH and Motility in the Upper Digestive Tract

Monogastrics - (**carnivores** and **omnivores**) tend to have low pH in the stomach (e.g. in the dog and pig, gastric pH range is usually 3 to 4):
Ion traps weak bases (adds a proton to form -NH3+ or >NH2+) - which delays absorption. Weak acids (adds a proton to form -COOH) are neutral when protonated and therefore are absorbed directly from the stomach.

Posterior fermenters - (e.g. **horses**) tend to have a higher gastric pH (of around 5.5) than most other species. The stomach is rarely empty in the horse. Because of it's small stomach (relative to its body size), the animal is nearly a continuous feeder.
Ruminants tend to have a slightly acid ruminal pH (diet dependent - increase in grain lowers pH).
In common production systems, ruminal pH may approximate 5.5 to 6.5. The rumino-reticular environment does not favor absorption of most drugs. However, drugs of sufficient lipid solubility will traverse the stratified squamous epithelium of the mucosa via passive non-ionic diffusion. Well-absorbed drugs include non-ionized forms of weak acids in the mildly acidic rumen content.
Abomasal (true stomach of **ruminants**) pH is typically around 3, which is similar to that of the stomachs of monogastrics. However, the flow of ingesta through the abomasum is more continuous than in the stomach of most nonruminants.



Proportions of nonionized and ionized forms of acetylsalicylic acid (pKa = 3.5) in biological fluids. Note - This pertains to upper digestive tract pH, as well as that of the intestine, blood,interstitial fluid, and urine.

Comparing Differences in Gastrointestinal Absorption Experimentally

To compare differences in absorption among species, you must have both oral and intravenous dosing data (plasma-concentrations vs. time postdosing) on the species of interest.

Differences in Respiratory Uptake

Birds in general are highly effective at moving air through their lungs and tend to come to equilibrium with gases in their environment faster than mammals. This makes them uniquely sensitive to gaseous toxicants!

Birds typically inspire into their air sacs, followed by flow through tubes (parabronchi) in the lungs that have great surface area (small outpouchings along their length) (no true flow into and out of alveoli) and then to the outside. A counter current mechanism (blood flow in the direction opposite that of air flow) is involved which also increases the efficiency of gaseous exchange. The mechanics of the system make dead space much less of an issue than in mammals. Thus, whooping cranes even have a large tracheal loop imbedded in their breast bone.

Birds are highly sensitive to carbon monoxide (CO) poisoning despite the lower sensitivity of their hemoglobin to CO-induced inhibition of oxygen-carrying capacity. As compared to mammals, the more efficient ventilation of birds increases their rate of uptake of inhaled toxicants. Note that coal gas (gas derived from coal) often contained toxic amounts of CO. In the USA, this gas has largely been replaced by the use of natural gas (rich in methane). The presence of CO in coal deposits lead to the use of the "coal miner's canary", as described below in a bulletin for miners published in 1916.

Birds and mice may be used to detect carbon monoxide, because they are much more sensitive to the poisonous action of the gas than are men. Experiments by the Bureau of Mines show that canaries should be used in preference to mice, sparrows, or pigeons, because canaries are more sensitive to the gas. Rabbits, chickens, guinea pigs, or dogs, although useful for exploration work in mines, should be used only when birds or mice are unobtainable, and then cautiously, because of their greater resistance to carbon monoxide poisoning.

Many experiments have shown that if a canary is quickly removed to good air after its collapse from breathing carbon monoxide it always recovers and can be used again and again for exploration work without danger of its becoming less sensitive. Breathing apparatus must be used where birds show signs of distress, and for this reason birds are of great value in enabling rescue parties to use breathing apparatus to best advantage (Burrell and Seibert, 1916).

2. Species Differences in Distribution

Role of Plasma Proteins

Unbound compounds in plasma are generally regarded as free to enter the tissues and exert an effect, while bound xenobiotics generally serve as a depot. Therefore, differences in protein binding among species can account for significant differences in potency of certain drugs and other toxicants.

The fraction of a xenobiotic bound in the plasma proteins is a function of the drug concentration, the protein concentration, the affinity of one for the other, and competition with other endogenous and exogenous compounds that may compete for binding sites. The health and plane of nutrition of the animal can sometimes influence plasma protein concentrations. For example, malnourished animals or parasitized individuals as well as animals with severe liver or kidney disease may have low serum albumin.

Displacement of drugs from binding sites (e.g. warfarin) by other drugs, is a major cause of adverse drug reaction in **human beings**. In part, this is because of the high protein bound fraction of warfarin and the common use of multiple drugs. It is also a result of the intended use of warfarin at a dose that has a limited effect on blood clotting, i.e. by design there is a significant amount of free drug in the blood which is able to enter the liver.

Thus, if the person has 95% bound + 5% free and only 1% is displaced by another drug (e.g., a sulfonamide), there will be a 20% increase in free warfarin (5 - 6%).

With most drugs, regardless of the species, animals are exposed at doses that do not cause saturation of plasma proteins. Nevertheless, with some drugs, such as sulfonamides, salicylates, and phenylbutazone, therapeutic levels bring about near-saturation concentrations and, as they increase, the percentage bound decreases. Such drugs may therefore have a tendency toward drug interactions in a range of species. Variability among species with regard to the extent of protein binding in the serum depends upon the specific xenobiotic and the doses involved. Salicylates exhibit marked differences among species with regard to binding to plasma proteins.

Although most drugs are bound primarily to albumin, some drugs, such as beta-adrenoreceptor blockers (oxyprenolol, propranolol), antiarrhythmics (lidocaine), and tricyclic antidepressants are bound primarily to alpha1-acid glycoprotein (α 1-AGP; an acute phase protein).

There is less α1-AGP in the serum than albumin, therefore, drugs that bind this protein may tend to exceed the serum protein binding capacity more often than those that bind to albumin.

Note - There may be considerable intra-species variation with regard to α1-AGP concentrations in the blood - which can greatly influence individual response to a range of xenobiotics. Therefore, individual variation among **dogs** with regard to response to drugs with an affinity for α1-AGP (lidocaine, oxyprenolol, propranolol), is much greater than with drugs with an affinity instead for albumin (digitoxin, phenytoin, and diazepam).

Body Fat

Marked differences exist among species, strains, and individuals with regard to the amount of body fat and its mobilization.
Some species of wildlife and domestic animals normally have periods of *marked mobilization of lipid stores*.
Birds - Egg laying, migration
Offspring may be disproportionately exposed via the yolk. Birds may sometimes experience acute toxicoses due to redistribution of persistent insecticidal compounds from the adipose tissue to the brain.
Mammals - Migration; winter starvation; lactation; estivation/hibernation.

Mobilization of fat can greatly reduce the availability of adipose tissues to serve as a depot for xenobiotics. For acute exposures this can increase the amount of xenobiotic in non-adipose tissues including the brain as well as sites of metabolism and excretion. For animals chronically exposed to lipid soluble metabolically-resistant compounds, mobilization of body fat can elevate plasma concentrations of the xenobiotic increasing the likelihood of toxicosis in the animal (or in it's developing or nursing offspring).

Absorption by the Embryo and Fetus: Separation of the Maternal and Fetal Blood

The number of layers that separate maternal and fetal blood influence not only the rate of passage of small proteins, but also that of a range of xenobiotics. The molecular size and polarity of the molecule may influence the rate of transfer from the dam to the offspring and back.

Placental Type	**Maternal Tissue**			**Fetal Tissue**			**Species**
	Endothelium	**Connective Tissue**	**Epithelium**	**Trophoblast**	**Connective Tissue**	**Endothelium**	
Epitheliochorial	+	+	+	+	+	+	pig, horse, donkey
Syndesmochorial	+	+	-	+	+	+	sheep, goat, cow
Endotheliochorial	+	-	-	+	+	+	cat, dog
Hemochorial	-	-	-	+	+	+	human, monkey
Hemoendothelial	-	-	-	-	-	+	rat, rabbit, guinea

3. Species Differences In Metabolism

Factors Intrinsic and Extrinsic to the Liver

Differences among species in the rate of metabolism by the liver are a function of factors intrinsic to the liver and factors extrinsic to the liver.
For most drugs, biotransformation is dependent primarily upon factors intrinsic to the organ, e.g. constitutive enzyme profile of the species and/or enzyme induction brought about by xenobiotics, including dietary components. In this case, biotransformation is restricted to the fraction of the drug that is free in the plasma.

The process in this case is termed *restrictive, non-flow dependent*.
For some drugs, however, (e.g. lidocaine and propranolol), the primary determinant in biotransformation by the liver is extrinsic, e.g. blood flow to the organ.
The process in this case is termed *non-restrictive, flow-dependent*.

Read: Introduction to the Toxicology of the Liver

Phase I Reactions

Phase I reactions involve enzyme-mediated changes in the xenobiotic molecule that typically cause it to become more water soluble (e.g., hydroxylation or epoxide formation by P450 enzymes; or hydrolysis by alcohol dehydrogenases).
Examples of Species Differences -
The anti-oxidants, butylated hydoxytoluene (BHT) and butylated hydroxyanisole (BHA) are potent inducers of epoxide hydrolases in mice but not in rats. In general, rats have low epoxide hydrolase activity relative to mice and rabbits.

Hydroxylation (at least of sulfonamides) occurs in **human beings** and **dogs**. Some hydroxy-metabolites are excreted by active renal tubular secretion, while others are conjugated with glucuronic acid before excretion.
Other Sources of Variation -
Differences among strains, sexes, ages, and individuals also exist.
Diet is a significant factor. Diets deficient in protein may caused greatly reduced P450 activity. This is believed to account for reductions in susceptibility to carbon tetrachloride in partially starved animals as compared to controls (**starved animals** less able to bioactivate CCl4 via P450 to highly reactive and toxic metabolites).

Phase II (Conjugation) Reactions

There are 6 major metabolic conjugation reactions in ***mammals*** - and these can be divided into two types: i) those deriving the required energy from an activated endogenous conjugating agent, most often a nucleotide; and ii) those where the xenobiotic undergoes metabolic activation before conjugation.

Reactions that Involve Activated Conjugating Agents	Reactions that Involve Activated Xenobiotics
Glucuronidation (Uridine diphosphoglucuronide = UDPGA)	Glutathione conjugation (Epoxides, alkyl, and aryl halides, nitro compounds, others)
Sulfation (3-phosphoadenosine, 5-phosphosulfate = PAPS)	Amino acid conjugation (Xenobiotic acyl-CoAs)
Acetylation (Acetyl-CoA)	
Methylation (S-adenosyl methionine)	

Acetylation

Acetylation of xenobiotics is catalyzed by N-aetylases and acetylcoenzyme-A. It is believed to be an ancient process, being found in **snails** and **turtles**. In **mammals**, *it is present at birth*. In some species, acetylation is an important aspect of sulfonamide metabolism.
Some species contain strains/individuals that are slow and others that are fast acetylators. The fast acetylators have an enzyme that is missing in the slow acetylators.
Fast-slow acetylation has been demonstrated in **human beings**, some species of **monkeys**, and **rabbits**.
Cats, including **domestic cats** and **lions**, as well as the **civet** (a member of the Viviridae, not the Felidae) are able to acetylate sulfadimethoxine. The fraction of a dose acetylated was 18% in the domestic cat, 48% in the lion, and 66% in the civet.
Dogs and related species (e.g. **hyena**) cannot N-acetylate sulfadimethoxine or sulfanilamide. Since acetylsulfanilamide tends to precipitate in renal tubules, the inability to produce the acetyl derivative tends to protect dogs against renal damage with this compound.
Dogs are unable to acetylate isoniazid, which predisposes them to isoniazid toxicosis.
Failure of **dogs** to N-acetylate aromatic amines results in their high susceptibility to methemoglobinemia following exposure to these compounds. With some xenobiotics, **dogs and related species** also sometimes exhibit such rapid de-acetylation that it falsely appears that acetylation never occurred.
Dogs acetylate the S-substituted cysteines that serve as penultimate intermediates in the conversion of glutathione conjugates to mercapturic acids.
Guinea pigs can acetylate a number of types of amines, but they are unable to acetylate the S-substituted cysteines. Thus, although they can form glutathione conjugates, they are unable to excrete mercapturic acids.
Sheep and pigeons may exhibit similar rates of acetylation and deacetylation.

Sulfation

Sulfation is important in that it is used by a range of species to make some types of xenobiotics (but not others) more water soluble and thus excretable.
Example - PAPS is used to sulfate aryl amines but not aliphatic amines.
Sulfation occurs in most species of animals including **invertebrates, fish, amphibians, reptiles, birds, and mammals**. For example, sulfation of phenols is a highly conserved and thus widely employed mechanism of detoxification.
Swine have low sulfotransferase activity, and thus little ability to conjugate xenobiotics to sulfate.

Phenol Conjugation to Sulfate and Glucuronic Acid in Various Species

Species	Percentage of Dose Conjugated		Ratio S/G
	Sulfate	Glucuronic Acid	
Human & old wld monkeys	80	12	7
New world monkeys	25	50	0.5
Rat & mouse	45	40	1.13
Cat	93	1	93
Pig	2	95	0.02

Percentage of Dose Conjugated

	Glucuronide		Sulfate	
Species	**Phenol**	**Quinol**	**Phenol**	**Quinol**
Human being	23	7	71	0
Rhesus monkey	35	0	65	0
Squirrel monkey	70	19	10	0
Rat tail monkey	65	21	14	0
Domestic cat	0	0	87	13
Ferret	41	0	32	28
Pig	100	0	0	0
Indian fruit bat	90	0	10	0
Guinea pig	78	5	17	0
Hamster	50	25	25	0
Rat	25	7	68	0
Gerbil	15	0	69	15
Rabbit	46	0	45	9

Sulfation and glucuronidation systems tend to balance one another, since similar functional groups are conjugated by the two systems. Sulfation generally involves enzymes with a high affinity, but low capacity to conjugate phenols. Conversely, glucuronidation enzymes generally have a low affinity but a high capacity for conjugating phenols.

Glucuronide Conjugation

Glucuronide conjugation is a major detoxification pathway for a range of xenobiotics.

For example, glucuronide conjugation is involved in metabolism of steroids, salicylates, morphine, and codeine.

Glucuronide conjugation occurs in most laboratory animals and man, but not hens or spiders. The **Gunn rat** is used in research as a model of "defective" glucuronyl transferase.

Cats (domestic shorthair, lion, lynx) have "defective" glucuronyl transferase (see below under cats).

Thus, cats, including **domestic cats, lions, and lynx**, as well as the civet are unable to glucuronidate 1-naphthyl-acetic acid.

Domestic cats form little or no glucuronide conjugates with phenol, naphthol or morphine, but they readily form glucuronides with bilirubin, thyroxin, certain steroids, and phenolphthalein.

Cats are highly susceptible to aspirin toxicosis (related to low glucuronide conjugation). The halflife of aspirin in cats is 3 - 4 times longer than in dogs.

Glutathione (GSH) Conjugation
GSH conjugation occurs in the cytosol by the action of GSH-transferases. This is an induceable process, unlike most other cytosolic conjugating enzyme systems. Induction of GSH transferases may be on the order of a two or three fold increase in activity.
Induction of GSH transferase activity varies among species.
The anti-oxidant, butylated hydroxyanisole (BHA) is a potent inducer of GSH transferases in mice but is less effective in **rats**.

Amino Acid Conjugation
Taurine conjugation occurs in many species, but is well developed only in **carnivores**.
Chimpanzees conjugate aromatic and heterocyclic carboxylic acids to glutamine.
Human beings conjugate benzoic acid to glycine (this combination = hippuric acid).

			% % of Dose excreted in 24 Hours as a Conjugate	
Compound	**Class**	**# of Species Tested**	**Glutamine**	**Glycine**
Phenylacetic Acid	Human Being		92 - 94	0
	Old World Monkeys	8	30 - 90	0.1 - 1.0
	New World Monkeys	3	64 - 80	1 - 10
	Lemurs	2	0	80 - 87
	Non-Primates	10	0	80 - 100
Indolylacetic acid	Human Being		10 - 21	0
	Old World Monkeys	3	32 - 53	0
	New World Monkeys	3	19 - 41	7 - 26
	Lemurs	2	0	14 - 49
	Non-Primates	8	0	25 - 70
ρ -Chlorophenylacetic acid	Human Being		92	0
	Rhesus Monkey		45	0.4
	Capuchin Monkey		36	1.4
	Rat		0	97
ρ -Nitrophenylacetic acid	Human Being		0	0
	Rhesus Monkey		0	0
	Rat		0	68

Note - Five conjugation reactions seem to occur only in **human beings** and **other primate species**. One of these involves the amino acid glutamine:
Glutamine conjugation of arylacetic and aryloxyalkyl acids (**human beings, apes, old & new world monkeys**).
The other four are:
N'-glucuronidation of certain methoxysulfonamides (**all primates**).
Quaternary N-glucuronidation of tertiary aliphatic amines (**human beings and apes only**).
C-glucuronidation of pyrazolone rings (**man and apes only**).
O-methylation of 4-hydroxy-3,5-diiodobenzoic acid (**human beings, old & new world monkeys**).

Common and Unusual Conjugation Reactions in Various Species		
Conjugating Group	**Common**	**Unusual**
Carbohydrate	Glucuronic acid (various animals)	N-Acetylglucosamine (rabbits)
	Glucose (insects and plants)	Ribose (rats, mice)
Amino Acids	Glycine	Glutamine (human beings, insects)
	Glutathione	Ornithine (many species of birds)
	Methionine	Arginine (ticks, spiders)
		Glycyltaurine and glycylglycine
(cats)		
		Serine (rabbit)
Acetyl	Acetyl group from acetyl-CoA	
Formyl		Formylation (dog, rat)
Sulfate	Sulfate group from PAPS	
Phosphate		Phosphate monoester (dogs, insects)

Metabolic Rates and Species Differences during Different Seasons -
Body temperature. **Homeotherms** vs. **poikilotherms**.

- Influences whether the species will be out and about, and thus potentially exposed, at various times of the year (climate - latitude - dependent).
- Influences metabolic rate, and thus the rate of metabolism and elimination of xenobiotics, at different times of the year.

Evaporation rates in summer vs. winter.

- Influences rate of elimination of volatile substances (may be greater in summer).

Differences in metabolism in different seasons.

- Especially important in animals that hibernate. Metabolism may slow, but fat mobilization may be marked over time, causing a xenobiotic to lose it's adipose tissue depot - and thereby increasing the opportunity for the liver to act on it.

The metabolic rates of **birds** is very high.

- Blood glucose is around 200 mg% in normal birds. Therefore starvation for comparatively short periods of time may result in death more often than in mammals. Birds that do not eat voluntarily may require feeding by hand, by tube, and/or parenterally.

4. Species Differences in Elimination

Renal Elimination -
The kidney of **birds** differs from that of most mammals. In birds, renal lobules are located throughout the organ. The different lobules are not readily separated from one another but instead are intermingled with their neighbors. In birds, the kidneys have a central vein, somewhat like the liver.
Birds have two types of nephrons, the short "reptilian type" which have no loops of Henle, and the long, medullary, "mammalian type" which have loops of Henle. The different types are coordinated through intermittent contractions of afferent arterioles, depending on the salt and hydration status of the individual.
Birds also have a renal portal system, in which much of the blood perfusing the kidney (50 to 75%) is derived

from the external iliac and sciatic veins. The fraction of blood from the common iliac vein that is diverted into the renal portal vein is determined by the degree of closure of the renal portal sphincter. This sphincter is under nervous control and has both adrenergic and cholinergic receptors. When the sphincter is relaxed and thus open, blood can bypass the renal portal system, going on into the posterior vena cava.

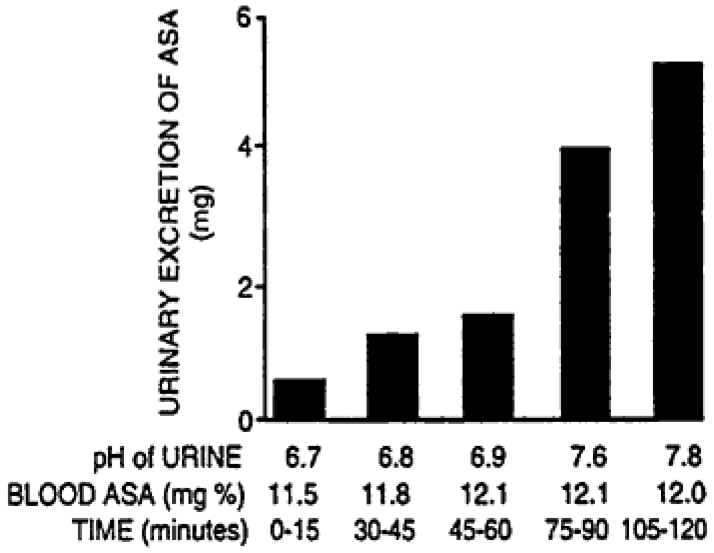
Birds, at least some strains of domestic fowl, have comparatively low glomerular filtration rates. As compared to mean GFR values of 2.5 to 5.1 ml/kg/min in cats and 3.0 to 4.2 ml/kg/min in dogs, GFR values in domestic fowl ranged from 1.4 to 4.7 ml/kg/min, with most values below 3. The primary nitrogenous excretory product in birds is uric acid, which is less water soluble than urea and which readily precipitates in renal tubules and eventually other sites in animals dehydrated for a range of reasons. The formation of crystals of uric acid results in a loss of it's osmotic activity, such that water reabsorption can continue. This contributes to the observation that dehydrated fowl can reabsorb 99% of the fluid filtered by the glomerulus. The low GFR and high reabsorption of water from avian excreta seems to increase their susceptibility to toxicoses caused by agents that normally leave via the urine, such as excess salts, water soluble drugs such as arsanilic acid, and heavy metals.

Urine pH (alkaline in **ruminants**, and **rabbits**, often acid in **carnivores**) influences the rate of elimination of specific xenobiotics via the urine. At least in part, this is because the rate of passive reabsorption under different pH conditions is influenced by the pKa (the pH at which a molecular site is half-ionized) as well as the lipid solubility. Molecules in the renal filtrate that are neutral and nonpolar are more likely to be reabsorbed than those that are charged and polar.

Ruminants tend to have a urine pH that is alkaline (pH of 8 - 9) as well as a high rate of urine output. These factors decrease the passive tubular resorption, and thus promote the elimination of sulfonamides.

Human urine pH generally is in the 5 to 7 range.

Dog urine varies in pH from 6 to 9.



Effect of urine pH on excretion of acetylsalicylic acid (aspirin = ASA) via the kidney. - Dog, male, 12 kg, hydrated with water (250 ml orally) 1 hr before the experiment. ASA (0.5 g orally) was given 45 min before the experiment. ASA (50 mg) in 0.9% NaCl in water (150 ml) was continuously infused during the experiment. At 20 to 25 min $NaHCO_3$ (0.5 g) was given intravenously. Urine collections were made at 15-min intervals from a bladder catheter.

Dogs have a relatively poor ability to excrete organic acids (their organic anion excretion system is poorly developed) - which increases susceptibility to the phenoxy herbicides, such as 2,4-D.

Elimination Via the Milk

The milk of cows tends to be slightly acidic (pH of 6.5 to 6.9) relative to the plasma (pH of 7.2 to 7.4), and it contains considerable milkfat (note many species have much more fat in their milk than cows).

Therefore, milk tends to concentrate basic, as well as fat soluble drugs and toxicants. This may result in relay of toxicants from cows, especially to beef calves and human beings with a high milk intake (e.g. infants).

The toxic principles of white snakeroot (*Eupatorium rugosum*), apparently partitions into milk preferentially such that lactating cows ingesting the plant are protected from poisoning, whereas nursing calves and human beings that ingest the milk are highly predisposed to poisoning.

Other Individual Species Characteristics/Differences of Importance in Clinical and Environmental Toxicology

Some of these Relate to Species Differences in Absorption, Distribution, Metabolism and Excretion (ADME)

General Considerations:

- Different species vary widely with regard to their likelihood of exposure to given toxicants (environments vary, food varies).
- Different species once exposed often vary widely in their susceptibility to various toxicants (different gastrointestinal environments, different enzymes involved in toxification or detoxification).
- Different species may manifest toxicosis due to a single agent in quite different ways.
- Sometimes, within a species different breeds may vary with regard to their susceptibility to a single toxicant.
- The use of adsorbents and cathartics is common to most species, but the other measures that should be used to terminate gastrointestinal absorption vary widely among species. For some species, emetics or enterogastric lavage are NEVER recommended.
- Appropriate antiarrhythmics vary among species.
- Appropriate anticonvulsants vary among species.
- Appropriate drugs for other purposes often vary among species.
- Drug dosages often vary among species.
- Some clinical pathology parameters (e.g. serum enzymes) vary widely among species.

Human Beings

- Uniquely sensitive to idiosyncratic reactions to chloramphenicol, which may cause irreversible aplastic anemia.
- Relatively sensitive to lead toxicosis; prone to decreased CNS function; and anemia may be associated with chronic exposure.
- The skin of swine and guinea pigs tends to give a rather good approximation of the absorption by human skin. However, there are marked exceptions, and data must be determined and compared among these species on a case-by-case basis.

Dogs

- Unlike man, fetal hemoglobin of dogs is the same as adult hemoglobin [fetus has decreased concentrations of 2,3,diphosphoglutarate (2,3-DPG)].
- Indiscriminate eating habits: Commonly consume garbage (source of bacterial and fungal organisms and toxins), dead animals (carrion = sources of bacterial organisms and toxins), lead objects, motor oil, rock salt, antifreeze, owner's or their own medications (especially chewable products) in huge quantities.
- Dogs occasionally ingest anesthetizing (and possibly lethal) doses of euthanasia drugs given to large animals (especially when they eat the viscera = frequently the first thing consumed by a carnivore). Often, such drugs are not well distributed in the body by the time that death occurs.
- Extreme differences in size among breeds - influences xenobiotic doses in 2 ways.
    - Size alone - often an animal eats all of a toxicant available. Whatever quantity is there, when ingested by a small dog, comprises a larger dose as compared to ingestion by a larger dog.
    - For some drugs, lower doses on a mg/kg basis have been recommended for large dogs than for smaller dogs.
- Aging rates vary among breeds - Chihuahua vs. great Dane.
- Susceptibility to selected toxicants varies among breeds.
    - Some collies are very susceptible to the anthelmintic ivermectin since the blood-brain barrier is not effectively in excluding the drug.
    - Some sight hounds such as greyhounds seem to be quite susceptible to some organophosphorus insecticides.
    - Some Bedlington terriers are prone to copper storage diseases > copper builds up > liver failure.
- Dogs pant (shallow, rapid respiration) to thermoregulate in warm surroundings which may alter respiratory exposure.

- Dogs are low to the ground, and carbon monoxide is slightly lighter than air, but dogs still tend to be more sensitive to carbon monoxide than man. Dogs may die before man from smoke inhalation.
- Canids are slightly more susceptible to the "canicide" Compound 1080; relay toxicosis can readily occur in canids.
- Dogs are quite susceptible to, and commonly ingest, brodifacoum and diphacinone (anticoagulant rodenticides).
- Dogs are quite susceptible to cholecalciferol (vitamin D3) containing rodenticides.
- Dogs are prone to eat methylxanthine-containing products such as caffeine tablets and chocolate in massive (toxic) quantities.
- Dogs often have an acid urine which contributes to their high susceptibility to sulfonamides (also, See acetylation above).
- Dogs are relatively susceptible to ethylene glycol and commonly ingest it.
- Dogs are relatively susceptible to onion toxicosis > Heinz body anemia. Note that, while human beings have only two exposed (reactive) sulfhydryl groups on the globin beta chains of their hemoglobin, dogs have four such sulfhydryls.
- Dogs are relatively susceptible to blue-green algae toxins.
- Dogs are comparatively susceptible to estrogen-induced aplastic anemia. (Cats given doses five times greater than those that caused aplastic anemia in dogs developed only mild stem-cell depression).
- Unlike hamsters and rabbits, dogs are susceptible to carbaryl-induced teratogenesis.
- **Dogs readily vomit.**
    - Preferred emetic: apomorphine.
    - Second choice: 3% hydrogen peroxide or syrup of ipecac.
- Enterogastric lavage can be used in dogs.
- Peritoneal dialysis can be used in dogs to enhance elimination of water soluble xenobiotics and/or to detoxify animals with renal failure.

Cats

- Most are more selective in their eating habits than dogs, but sometimes still consume toxic quantities of human medications and occasionally massive amounts of chewable veterinary drugs - e.g., d,1-methionine, a urinary acidifier.
- Fastidious grooming habits tend to increase oral exposure to substances on the skin.
- Domestic cats are a species well adapted to an arid environment, with a rather concentrated urine which may predispose them to poisoning by certain water soluble toxicants. This may play a role, for example, in their considerable sensitivity to ethylene glycol toxicosis.
- The number of reactive sulfhydryl groups on the beta chain of the globin molecule of the hemoglobin molecule of various species is correlated with the susceptibility of the molecule to oxidative injury. In contrast to human beings (who have two) and dogs (that have four), cats have eight or more reactive sulfhydryls on their globin component. The hemoglobin of cats is therefore extremely sensitive to oxidative stress > readily forms methemoglobinemia (normal hemoglobin with Fe^{++} converted to methemoglobin with Fe^{+++} & Heinz bodies. Heinz bodies are denatured hemoglobin molecules that become attached to the inner surface of the erythrocyte cell membrane, thus causing it to be deformed. The deformed red blood cells are then prematurely "picked off" and destroyed by the spleen, thus resulting in Heinz body anemia. **Note** - Limited numbers of Heinz bodies are seen in normal cats, and the feline spleen is less able to remove defective erythrocytes than in other species, so Heinz body-bearing cells persist longer in the blood of cats than in other domestic species.
    - High susceptibility to acetaminophen is presumed to be a function of limited glucuronide conjugation (and subsequent depletion of GSH) coupled with subsequent oxidative injury in erythrocytes leading to oxidation of hemoglobin (Fe^{++}) to methemoglobin (Fe^{+++}). The usual syndrome seen with acetaminophen toxicosis in cats (methemoglobinemia) differs from that in human beings and dog (species that more often develop liver failure).
    - Other substances that may cause methemoglobinemia in cats include: benzocaine, methylene blue (high enough doses), phenoazopyridine, para-aminobenzoic acid, and onions.
- Feline erythrocytes have a considerably shorter life-span than those of most other species. The mean life span ranges from 66 to 79 days, and this may increase susceptibility to "depression anemias", such as that associated with chloramphenicol exposures. Chloramphenicol-induced anemia is nevertheless reversible in cats (and dogs).
- Cats are very sensitive to arsenic including sodium arsenate insecticides.
- Cats are highly susceptible to organochlorine insecticides of all types.
- Cats seem to be more susceptible than most species to pyrethrin and pyrethroid insecticides.
- Persians seem to be even more susceptible than other breeds of cats to insecticidal dips.

- Cats are quite susceptible to organophosphorus insecticides.
- Feline RBCs are extremely low in cholinesterase. Therefore, almost all of whole blood cholinesterase activity is from plasma. Consquently, blood cholinesterase is a sensitive indicator of exposure, but it may be depleted to "zero" activity even with only subtoxic exposures.
- Cats have a low tolerance for lidocaine as an antiarrhythmic agent. Signs of toxicosis include drowsiness, emesis, nystagmus, tremors, and seizures.
  - Usually a b-blocker is used to treat cats for serious tachyarrhythmias, and atropine for bradyarrhythmias.
- **Cats readily vomit.**
  - There is **no** safe and effective dose of apomorphine in the domestic cat.
  - Preferred emetics for cats = 3% hydrogen peroxide, or syrup of ipecac; some veterinarians like xylazine = Rompun ®. Note: depression from xylazine can be reversed with yohimbine or similar drugs
- Enterogastric lavage can be used for cats.
- Peritoneal dialysis can be used for cats.

Ferrets

- Ferrets have more submucosal glands in their bronchial walls and an additional generation of terminal bronchioles. These features are more similar to the airways of human beings than those of dogs.
- Female ferrets are induced ovulators and, in the absence of males, mature females experience endogenous estrogen-induced bone marrow suppression and death.

Swine

- Swine readily vomit.
- As compared to other domestic animals, the morphology and physiology of swine tend to make the species a preferred model for extrapolation to human beings
  - Used increasingly in cardiovascular and pulmonary and digestive system research.
  - Pulmonary function criteria in swine are similar to those of human beings. Also, airway diameters are similar in size. However, the complex turbinates of swine filter out particulates more effectively than in human beings.
- Fetal hemoglobin is the same as adult hemoglobin.
  - Piglets are still very sensitive to carbon monoxide - perhaps due to the difference in 2,3-DPG
- Ingestion of feces by young (<5-week-old pigs) provides them with vitamin K which offsets the requirement for supplementation (as well as the associated hypoprothombinemia and lethal hemorrhage).
- Swine are extremely susceptible to poisoning by anticoagulant rodenticides.
- Hydrogen sulfide gas is a relatively common problem in pigs raised in captivity > lethal to man as well and acts rapidly in any species > respiratory paralysis.
- Some strains of swine commonly react to halothane by developing malignant hyperthermia.
- Swine are very sensitive to clay pigeon (contain phenolic compounds) poisoning.
- Diesel fuel used as a vehicle for topically applied insecticides causes abortion in swine.
- Swine are relatively susceptible to blue-green algae toxins.
- Swine are highly sensitive to infertility and signs of estrogenism caused by the mycotoxin zearalenone.
- In response to exposure to toxic concentrations of the mycotoxin fumonisin in feed, pigs develop pulmonary edema, mild liver and pancreatic damage, and possibly immunosuppression.
- Swine are very sensitive to perirenal edema and nephrosis from ingestion of pigweed (*Amaranthus retroflexus*).
- Swine are prone to congestive heart failure as a result of exposure to gossypol.
- Swine are highly sensitive to water deprivation/sodium ion toxicosis.
- In swine, phenylarsonic feed additives cause demyelination > paralysis; and arsanilic acid (ρ -aminobenzenearsonic acid) may cause blindness.
- Swine are relatively tolerant of lead.
- Swine readily vomit. Emetic of choice in pigs: 3% hydrogen peroxide, which can be given slowly via the nares. **Note** - Apomorphine is ineffective in swine.
- Activated charcoal administration. Swine can be given activated charcoal via the snout (slowly). Hold animal with a snare, rinse with water when done.
- Enterogastric lavage is not practical + concern re potential distension and rupture of the spiral colon.
- Large herds may necessitate triage and may make getting enough activated charcoal or antidotes difficult.

- For topical exposures, swine can be crowded together, dusted with powdered detergent and rinsed thoroughly with a hose.

Cattle

- Energy metabolism is quite different in ruminants than in non-ruminants. Ruminants rely on short chain free fatty acids as their principle energy source. Blood glucose concentrations are normally around 50 mg/dl.
- In grazing situations, food is typically low in energy, and thus must be ingested in high volumes.
- Like other grazing animals, cattle ingest considerable amounts of soil.
- Like other herbivores, bovine urine is alkaline.
- Excretion of toxicants may sometimes contaminate milk (aflatoxin; white snakeroot toxins) or milkfat (persistent organochlorine insecticides).
- May be unable to market milk with residues in milkfat exceed tolerances (and some tolerances can be lowered by regulations).
- Producers who cannot sell milk go broke fast.
    - e.g., heptachlor epoxide residues caused major economic losses several years ago in Arkansas, Missouri, & Oklahoma.
- Bulls and exotic breeds of either sex are extremely sensitive to chlorpyrifos - 7 mg/kg topically can be lethal to mature bulls - vs. cats which are also sensitive but survive at up to 40 mg/kg per os.
- In adult ruminants, organic arsenical feed additives cause typical arsenic (GI, shock syndrome).
- Cattle are very sensitive to acute lead toxicosis. In the past, cattle commonly ingested lead in used motor oil; still eat storage batteries, old paint, etc.
- Cattle are very susceptible to molybdenum toxicosis/copper deficiency.
- Although cattle can vomit, they do not do so with ease, and no effective emetics have been marketted.
- Enterogastric lavage is **not** practical.
- Rumenotomy is done, but is time consuming and somewhat stressful. It is usually not practical for large numbers of animals.
- Rumen lavage is hard work but can be done using either a very large stomach tube or a trochar. Must have running water. Trochar runs some risk of peritonitis.
- Can bathe animals in herds by crowding them together in a pen and washing with power hose and powdered detergent.
- Obtaining activated charcoal in a large enough amounts to treat herds can be a problem. Commonly recommend 1 #/head. Need to ensure 24-hour access ahead of time! Same problem exists with 2-PAM and other antidotes. Regional antidote depots are a good idea: veterinarians are responsible to rapidly replace whatever is used.

Sheep

- Sheep are very susceptible to copper toxicosis/molybdenum deficiency > liver failure > release of copper > hemolysis, and terminal anemia and renal failure.
- Similar to cattle in many ways but different in others. Similar to cattle with regard to emetics and methods of lavage.

Goats

- Eastern states - Commonly eat mountain laurel (*Kalmia*), *Rhododendron*, and similar plants.
- Somewhat like sheep but tend to be much more independent and inquisitive.
- For most toxicoses, therapy considerations in sheep and goats are much like those in cattle.

Horses

- Do **not** recommend emetics - weak stomach may readily rupture.
- Oral antibiotics commonly cause overgrowth of *Clostridia* > lethal enterocolitis.
- Very sensitive to ionophore feed additives/coccidiostats, such as monensin > heart failure.
- Very sensitive to **thiaminase-containing plants**, such as horsetail (*Equisetum*) and brackenfern (*Pteridium*) > neurologic deficits.
- Very sensitive to, and display a unique lesion in response to the mycotoxin fumonisin in moldy corn > leukoencephalomalacia (also develop liver damage; and may die from liver failure).

- Very sensitive to atropine-induced colic > can be life-threatening. Use atropine only in **serious** cases of OP or carbamate insecticide toxicoses in horses and give **in fluids while ausculting abdominal viscera > avoid cessation of motility !!!**
- **Vitamin K3** > single **injection** at recommended dose > **lethal nephrosis** (injectable no longer marketed).

Rabbits

- Rabbits "must" consume their own feces unless supplemented with compensatory vitamins.
- Some strains have high atropinase, which protects them from toxicosis caused by atropine-containing plants such as *Atropa belladonna*. In such individuals, therapy for organophosphorus insecticide toxicosis may necessitate comparatively high doses of atropine (use with care, not all strains have high atropinase).
- Significant crystalluria is normal in rabbits which have a rather alkaline urine (pH 8.2). Phosphate and carbonate crystals predominate. Urine is normally turbid and cloudy yellow to red-brown.
- Do not recommend emetics - weak stomach may readily rupture.
- Oral antibiotics commonly cause overgrowth of *Clostridia* > lethal enterocolitis.

Guinea Pigs

- Young guinea pigs are much larger and more mature when born than are rats and mice.
- Susceptible to antibiotic-induced overgrowth of *Clostridia* > lethal enterocolitis.
- Guinea pigs are extremely sensitive to 2,3,7,8-tetrachlorodibenzodioxin (TCDD).
- Unlike hamsters and rabbits, guinea pigs are susceptible to teratogenesis induced by carbaryl.
- Guinea pigs are known for their ability to methylate histamine and nicotine, both reactions being catalyzed by the enzyme, azaheterocycle N-methyltransferase. Nicotine is a weak base and methylation of the pyridil nitrogen atom results in the presence of a charge at both nitrogens at physiologic pH. This increases water solubility and urinary excretion.
  - Guinea pigs are sometimes used to study the consequences of methylation of other xenobiotics.
- Cannot vomit.

Rats

- Have no gallbladder.
- Different capacities of DNA repair of various tissues have been explored in the rat.
  - In rats, a single high dose of dimethylnitrosamine induces kidney, but not liver, cancer because of the capability of liver repair enzymes to remove the alkylated DNA.
  - Similarly, ethylnitrosourea causes formation of DNA adducts in the liver, kidney, and brain, but because of the limited DNA repair capacity in brain tissue, the animals often develop cancer there whereas, they rarely develop renal cancer, and almost never develop cancer of the liver.

Mice

- After several hundred bioassays, it has become apparent that the B6C3F1 mouse is much more sensitive to exposure to a number of carcinogens than is the Fisher 344 rat (these two species have been used most widely in bioassays of chronic chemical exposure).
  - For example, of 85 chronic bioassay studies, the mice developed hepatomas in 45 studies, while the rats did so in only 15 studies.
  - The Nutrition Foundation ad hoc review panel concluded that the mouse, unlike the rat, develops tumors from agents found to be non-genotoxic in mutagenesis assays. Therefore, it was suggested that the mouse may possess more pre-initiated cells in the liver, and, therefore, the non-genotoxic toxicants are simply acting as tumor promoters. If this theory is valid, the question that remains is whether human beings have many or few pre-initiated cells (whether various human beings resemble the mice or the rats).

Woodchucks = Groundhogs = *Marmota monax*

- May have woodchuck hepatitis virus (WHV), which is a close relative of human hepatitis B virus (HBV).
  - Woodchucks with chronic active hepatitis induced by WHV are predisposed to hepatocellular carcinoma (similar to human beings with HBV).

  - Chronic carriers of WHV are available in nature and are not expensive to maintain in captive colonies.
  - Recent epidemiologic studies suggest that, if human exposure to aflatoxin causes liver cancer, "it almost always does so in the presence of HBV" (Bruce, 1990). Therefore, the woodchuck may be a species of choice for future studies of aflatoxin and its bioactivation/detoxification/elimination in the presence and absence of virally-induced chronic active hepatitis.

Birds

- See the section above on Metabolic Rate.
- In some species the crop is a major storage site of food where it is moistened and softened before passing into the remaining digestive tract. In others, such as geese, the esophagus is a site of considerable storage. Geese are therefore predisposed to local damage in the esophagus from damage induced by direct acting toxicants, such as the more toxic trichothecenes.
- Some species have a gizzard which has a highly muscular wall and a thick stratified squamous mucosa. In this organ, grinding of the food occurs in the presence of small stones. This can wear down solid toxicants, such as lead objects and the seeds of toxic plants, thus increasing their surface area and hence, their bioavailability and toxicity.
- The amino acid used by many species of birds to conjugate aromatic and heterocyclic carboxylic acids in ornithine.
- Birds tend to be much more tolerant than mammals to the acute effects of DDT. Nevertheless, falcons, bald eagles, brown pelicans, and mallard ducks were susceptible to DDT-induced eggshell thinning. By contrast, gallinaceous species (chickens, etc.) were resistant to this effect.
- Chickens are highly resistant to carbon tetrachloride toxicosis.
- Ducks, especially ducklings, are highly sensitive to aflatoxin and sometimes serve as a sentinel species.
- Waterfowl commonly develop botulism. When they die, their bodies serve as anaerobic substrates for production of more toxin by *Clostridium botulinum*, and when fed on by maggots, which in turn are eaten by other waterfowl, a viscious cycle occurs which can result in the deaths of thousands of the birds.
- See section above on Renal Elimination.
- See section above on Differences in Respiratory Uptake.
  - Caged birds are very sensitive to gases and particulates released from overheated Teflon or Silverstone cookware > deaths occur at concentrations of breakdown products in the air that are subtoxic or minimally toxic to other species.
  - There may be reason to be concerned with regard to exposure to volatile vehicles used indoors to apply household pesticides or dip solutions to dogs or cats.
- Many bird species are highly sensitive to organophosphorus insecticides.
  - Organophosphorus insecticides such as malathion are detoxified by aliesterases and carboxylesterases which induce hydrolysis of the compound. Many bird species have comparatively low levels of these esterases which causes them to be comparatively sensitive to malathion.
  - Thus, diazinon granular insecticide (an OP) is extremely toxic to waterfowl and some passerine species.
  - Cage birds may be extremely sensitive to chlorpyrifos.
- The adult hen is susceptible to organophosphorus-induced delayed neuropathy, and it manifests the syndrome with a markedly alterred gait. This has resulted in it's use in bioassays for this effect.
- The structure of the digestive tract precludes vomiting in most species. Some species, however, seem to be able to voluntarily eliminate the contents of the upper digestive tract (e.g. vultures). No emetics known. Most cage bird species have a crop which can be lavaged by a skilled veterinarian. Activated charcoal can be given by crop gavage.

Reptiles

- Poikilothermic to semi-warm blooded: when body temperature is reduced, metabolism and elimination may be greatly slowed.
- The primary nitrogenous excretory product is uric acid (see section above on Renal Elimination, especially the parts that pertain to birds).
- Urate crystals cause visceral gout and renal constipation (brought on by a buildup of uric acid crystals). This can result from an excess of protein or organ meats in the diet.
  - The buildup of uric acid in the animal may lead to severe liver failure and granuloma formation.

  - Reptiles with infectious diseases often drink less water than normal. This, coupled with their treatment, predisposes them to antibiotic toxicoses. For example, therapy with gentamicin must often be accompanied by fluid therapy to avoid renal tubular degeneration, which slows excretion of uric acid and thus, contributes to visceral gout.
  - Sulfonamide toxicosis in reptiles may be accompanied by similar visceral gout.
  - Certain tortoises have been known to survive after eating both azalea (*Rhododendron*) and oleander (*Nerium oleander*) leaves in quantities that would rapidly prove lethal to sheep or goats weighing a hundred fold more than the tortoises.

Amphibians

- Two-phase "amphibious" life cycle of most species results in exposure of eggs, embryos, and tadpoles via the water; of tadpoles via microscopic plants (e.g., green algae) (and sometimes zooplankton) in the water; and adults via the land and air as well as via the food chain (depending on the makeup of their diet - often insects; vertebrates).
- As compared to mice, frogs are 22 times as tolerant of the organophosphorus compound paraoxon. They are also more tolerant of the carbamate eserine, another cholinesterase inhibitor. This is an apparent result in differences in the structure of amphibian cholinesterases as compared to those of mice.

Fishes

- The gills are major organs of respiration and elimination.
- Kidneys vary among fish species, but often include a kidney primarily for urine production, and a head kidney, which functions more like bone marrow of mammals. Sometimes the two types of kidneys are joined together.
- Fishes breathe water, hence the resultant high level of exposure of lipid membranes of the gills to a range of lipid soluble compounds results in some partitioning into the fish; and if the compound is resistant to biodegradation, accumulation in body lipids results.
- Often uptake of persistent halogenated compounds by fish is greater via the food than via absorption across the gills. Predatory fish are exposed both via the water and, especially, from ingestion of contaminated lipids of lower members of the food chain.
- Fish are often highly effective in glucuronidation and sulfation of xenobiotics.
- Glutathione-S-transferases have been found in many terrestrial species, including birds, reptiles, and amphibians, insects, and plants. The lack of GSH-transferases in fishes suggests that the enzymes evolved to protect terrestrial organisms from oxidative injury and xenobiotics in the food and air. Aquatic organisms are bathed in a rich source of nucleophilic material, water, that can hydrolyze many reactive compounds, thus, reducing their toxicity.
- Freshwater fishes have to eliminate excess water. Consequently, they may be less prone to bioaccumulate water soluble toxicants than terrestrial organisms (the latter are more dehydrated).
- Saltwater fishes have to conserve water and eliminate excess sodium.
- Different species of fishes live at different temperatures, and oxygen tensions, and have varied diets.
- Bottom dwellers tend to have higher mixed function oxidase activities than do fishes that liver in the upper water column. This may be an evolutionary response to the greater exposure of the former to lipid soluble toxicants at the interface of the water and sediment.

Arthropods

- Crustaceans *Daphnia pulex* may produce up to 13 x 10^{12} offspring.

- Insects
- A single pair of houseflies breeding from April to August is able to produce 191 x 10^{18} offspring.
- Organophosphorus insecticides such as malathion are more readily hydrolyzed by mammals than by insects, which have lower levels of esterases. This is one mechanism of selective toxicity.

- Arachnids The amino acid used by some arachnids to conjugate aromatic and heterocyclic carboxylic acids in arginine.

Earthworms

- May accumulate extremely high concentrations of metals (i.e. lead at 330 ppm; zinc at 670 ppm) which would be lethal to mammals.
- Earthworms may be important in the environmental conversion of DDT to DDE. The concentrations of DDE in earthworms, when consumed by birds, may be sufficient to result in eggshell thinning.

Molluscs

Slugs (*Agriolimax reticulatus*) may bioaccumulate diazinon to concentrations (i.e. 400 ppm) that may be toxic to animals that prey upon them.

Coelenterates

- Polyps and jellyfish have both ectoderm and entoderm, as well as the "first" glandular structures.
- They also have connective tissues in the form of mesoglea; and wandering phagocytic cells.
- They have only one opening, which serves as the mouth and anus.
- Among the *Coelenterata*, the cnidarians have tentacles; whereas the ctenophorans have colloblasts instead.
- They have no distinct respiratory or excretory systems.

Sponges (*Porifera*)

- They lack true musculature and a nervous system.
- They generally are sessile marine organisms, but some freshwater species exist.
- Tissues in sponges are perhaps the simplest of all animals and plants.
- They have wandering phagocytic cells.

Incomplete List of Teratogens Used in Clinical Medicine

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Incomplete List of Teratogens Used in Clinical Medicine

Chemical	Dosage
Acetazolamide	0.6% (in diet)
ACTH	5 mg q 6 h/3 days
Actinomycin D	25 - 100 mcg/kg
Alcohol	1.0 - 210 gm/kg
Aldosterone	0.05 mg/day
Amantadine HCl	10 mg/kg
Aminophylline	100 - 200 mg/kg
Aminopterin	0.1 mg/kg
Anesthetics	-
Antibodies	-
Apomorphine	0.025 mg/embryo (chick)
Barbituric Acid	0.16% (mice) (in diet)
Busulfan	18 - 34 mg/kg
Caffeine	75 - 150 mg/kg
Chlorambucil	8 - 12 mg/kg
Chloramphenicol	100 - 200 mg/kg
Chlortetracycline	10 mg/kg
Colchicine	1 - 2 mg/kg (monkey)
Cortisone	-
Coumarin Derivatives	4 mg/kg (mice)
Dextroamphetamine Sulfate	1 mg/kg
Diazepam	200 mg/kg
Diethylstilbestrol	10 - 42 mg
Dimethyl Sulfoxide	4.0 ml/kg
Diphenylhydantoin	75 - 150 mg/kg (mice)
Disulfiram	100 mg (in diet)
L-Dopa	10 mg/kg
Epinephrine	1 - 50 mcg

Fluorouracil	12 - 37 mg/kg
Griseofulvin	50 - 500 mg/kg
Hypervitaminosis A	35,000 I.U.
Imipramine	15 mg/kg
Isoniazid	-
Lithium	212 mg/kg hen 85 mg/kg
Marihuana	4.2 mg/kg
Meclizine	20 - 80 mg/kg
Methaqualone	0.8% (in diet)
Methotrexate	10 mg/kg (mice)
Nitrous oxide	50% (by inhalation)
Noradrenalin	25 mcg/embryo
Phenobarbital	0.16% (mice) (in diet)
Physostigmine	0.05 - 15.0 mg/embryo (chick)
Pilocarpine	3 - 12 mg/embryo (chick)
Prednisolone	2.5 mg/kg
Prochlorperazine	2.5 - 10 mg/day
Reserpine	1.5 mg/kg
Salicylate	300 mg/kg
Sulphonamides	50 mg/kg
Tetracycline	40 - 80 mg/kg
Tolbutamide	300 mg/day

Rat data unless otherwise noted. From Shepard (1976)

Update on Tobacco (Nicotiana) and Human Health Concerns, Imidacloprid

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Nicotine

> Smoking and "pharmacologic" doses of nicotine accelerate heart rate, elevate blood pressure, and constrict skin blood vessels (Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Dubuque: Kendall/Hunt Publishing Company, 1984; 480. - Available from amazon.com -).

Anabasine

- *Nicotiana glauca* - 99% of total alkaloid is anabasine (Cheeke and Shull, 1985).
- Case report - One heifer consuming *N. glauca* had detectable anabasine levels in liver, urine, and rumen contents. No nicotine was detected. Nicotine and anabasine levels from a fresh plant revealed levels of 2 and 1430 ppm respectively (Plumlee KH, 1993).
- Anabasine binds to nicotinic binding sites but is less potent than nicotine (Plumlee KH, 1993).
- Nicotine, anabasine, and cotinine (metabolite of nicotine) cause direct and specific inhibition of aldosterone synthesis (in freshly isolated rat adrenal cells) via enzymatic blockade. this would be thought to activate renin-angiotensin system *in vivo* and this mechanism might then contribute to the cardiovascular damage that occurs with long term tobacco use (Skowronski RJ, 1994).

Smokeless Tobacco

- Oral cells, peritoneal macrophages, and hepatic mitochondria and microsomes produce reactive oxygen species following *in vitro* incubation with aqueous extract of smokeless tobacco (Bagchi M, 1996).
- High doses of smokeless tobacco extract reduced pre- and post-weaning offspring weight gain and increased fetal mortality in rats exposed during gestation. Smokeless tobacco at low dose had the opposite effect so that these offspring's weights exceeded control weights (Paulson RB, 1994).
- *In vitro*, nicotine inhibits the growth of gingival fibroblasts and their production of fibronectin and collagen, while also promoting collagen breakdown. Nicotine may itself augment the destruction of the gingival extracellular matrix occurring during periodontal inflammation associated with smokeless tobacco (Tipton DA, 1995).
- Inhibition of the aerobic antimicrobial functions of neutrophils and monocytes by nicotine may alter the microbial ecology of the oral cavity, and this might be one mechanism by which nicotine compromises the oral health of users of tobacco products (Pabst, 1995).

Tobacco Smoke

- The nitrosamine NNK is produced in tobacco smoke from nicotine (Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Dubuque: Kendall/Hunt Publishing Company, 1984; 203. - Available from amazon.com -).
- DNA adducts of carcinogenic polycyclic aromatic hydrocarbons have been demonstrated in RBC's of smokers (Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Dubuque: Kendall/Hunt Publishing Company, 1984; 222. - Available from amazon.com -).
- 30% of all deaths in the U.S. result from smoking (this includes not only lung cancer, but also cancers of the bladder, GI tract and upper respiratory tract).
- Nonsmoking adults normally do not have more than 1% carboxyhemoglobin, while heavy smokers can be as high as 5 - 10% (Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Dubuque: Kendall/Hunt Publishing Company, 1984; 344. - Available from amazon.com -).
- Smokers have increased alveolar macrophages in an activated state, but these macrophages seem to have decreased phagocytic and bactericidal activity (Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Dubuque: Kendall/Hunt Publishing Company, 1984; 379. - Available from amazon.com -).

- Smokers who inhale radon or asbestos fibers increase their risk of developing lung cancer severalfold (Osweiler G. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Dubuque: Kendall/Hunt Publishing Company, 1984; 452. - Available from amazon.com -).
- Tobacco plants exposed to mercury chloride solution or mercury vapor accumulated mercury in the roots and/or shoots (Suszcynsky EM, 1995).
- Smokers are more slender and have a lower bone density than nonsmokers. Smokers have poorer oral hygiene and less teeth than their nonsmoking counterparts (Johnston JD, 1994).
- Cigarette smoke condensate of two different brands was assayed. The most relevant elements in cigarette smoke condensate based on concentrates and toxicity were arsenic, cadmium, and lead (Krivan V, 1994).
- Because the smoker of lower nicotine cigarettes tends to smoke more intensely and to inhale the smoke more deeply than the smoker of plain cigarettes, the peripheral lung is exposed to higher amounts of nitrogen oxides, nitrosated compounds, and lung-specific smoke carcinogens (Hoffmann D, 1996).
- Rats exposed to pure nicotine in inhalation chambers for 20 hours per day, 5 days per week, and over 2 years had no harmful effects, except for a reduction in body weights compared to controls (Waldum, 1996).
- The offspring of pregnant mice exposed to cigarette smoke in a smoking machine for 10 minutes 3 times per day showed dose related retardation in embryonic growth which was more marked with exposure on days 0, 1, and 2. No difference was seen with higher or lower tar cigarettes (Seller, 1995).
- Neither nicotine nor its metabolites increased the frequency of mutations in the Salmonella mutagenicity assay, or the frequency of sister chromatid exchanges in Chinese hamster ovary assays (Doolittle, 1995).

Imidacloprid

- Active ingredient of Advantage ® by Bayer.
- It is a chlorinated derivative of nicotine. LD_{50} > 2000 mg/kg.
- Imidacloprid binds to nicotinic receptors; these receptors are more common in insects than in other animals (Moffat, 1993).
- Persistent activation of the nicotinic receptors leads to an overstimulation of cholinergic synapses and hyperexcitation, convulsions, paralysis, and death of the insect (Bloomquist, 1995).

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Molybdenum Toxicosis - Copper Deficiency, Copper Toxicosis, Copper Toxicosis - Molybdenum Deficiency - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Monensin - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Monkshood - ***Aconitum*** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Monterey Cypress - ***Cupressus Macrocarpa*** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Morning Glory - ***Convolvulus*** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Muscarinic - Histaminic Mushrooms - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Muscarinic Toxicants, Introduction to - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Mushrooms - Gastrointestinal, Hepatotoxic, Nephrotoxic, Neurotoxic, Cyclopeptide - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Mushrooms - General - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Mushrooms - Hallucinogenic Indoles - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Mycotoxicoses Introduction - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

N

Naphthalene - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Narcissus **- Daffodil, Jonquil** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

Nephrotoxic Antibacterial Agents - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nephrotoxic Metals - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nephrotoxicoses and Oxalate Excretion - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Nerium* - Oleander** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nettles - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Neuromuscular Blocking Agents - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Nicotiana* spp. - Tobacco** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nicotine - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nightshade group - *Solanum* spp - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nitrate - Nitrite - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nitrofuran Toxicosis - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nitrogen Oxides (Silo Filler's Disease) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nitrosamines - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nolina - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Nonsteroidal Anti-Inflammatory Agents - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
North American Poisonous Snakes - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

O
Oak - *Quercus* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Ochratoxins - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Oleander - *Nerium* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Oligomeris* - Desert Spike** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Onion (*Allium*) Poisoning - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Opiates and Opioids - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Organochlorine Insecticides and Diphenyl Aliphatics - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Organophosphorous - Induced Delayed Neuropathy - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Organophosphorus and Carbamate Insecticides - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Organotin Compounds - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Other Agents Causing Nephrotoxicoses and Oxalate Excretion - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Other Agents that Cause Acidosis - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Other Estrogenic Toxicants - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Other Nephrotoxic Antibacterial Agents - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Other Nephrotoxic Metals - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Overheated Polytetrafluoroethylene - Teflon or Silverstone - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Overview of Toxicants that Affect Neurotransmitters - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Oxytropis* and *Astragalus* - Locoweeds** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

P
Pancytopenia, Estrogen - Induced, in the Ferret - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Panicum* spp. - Panic Grasses** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Paraquat (A Dipyridyl Herbicide) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Partridge Pea (*Cassia fasciculata Michx*.) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Patulin and Citreoviridin - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Pennyroyal Oil - Ketone Pulegone - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Pentachlorophenol - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Persea Americana* - Avocado** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Petroleum Distillate Poisoning, Crude Oil - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Phenolics and Coal Tar - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Phenothiazine (Thiodiphenylamine) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Phenoxy Herbicides - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Phenylarsonics - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Phoradendron* spp. and *Viscum* - Mistletoe** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Phosphorus - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

***Physalis* - Ground Cherry** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Phytolacca* - Pokeweed** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Pieris* - Japanese Pieris** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Pigweed - *Amaranthus* spp. - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Pinus* - Pines** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Plants of the Araceae Family - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Podophyllum Peltatum* - Mayapple, Mandrake** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Poison Hemlock - *Conium* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Pokeweed - *Phytolacca* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Polybrominated Biphenyls (PBBs) and Biphenyls (PCBs) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Polychlorinated Dibenzodioxins, Highly Chlorinated Naphthalenes and Related Halogenated Aromatics - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Polytetrafluoroethylene, Overheated - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Privet - *Ligustrum Vulgare* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Propylene Glycol Antifreeze - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Pteridium Aquilinum* - Bracken Fern** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Puncture Vine - *Tribulus* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Pyrethrum and Pyrethroids - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

Q
***Quercus* - Oak** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

R
Radiation Toxicology - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Ragwort - Groundsel, *Senecio* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Ranunculus* spp. - Buttercups** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Rattlebox - *Crotalaria* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Rayless Goldenrod - *Isocoma Wrightii* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Red Maple (*Acer Rubrum*) Poisoning - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Rheum* - Rhubarb** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Rhododendron - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Ricinus Communis - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Robinia - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Rotenone - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Rubberweed - Bitterweed - *Hymenoxys* spp. - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Russian Napweed and Yellow Star Thistle - *Centauria* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

S
Salicylates and Aspirin - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Sambucus* - Elder, Elderberry** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Sandburs - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Saponaria* spp.** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Sarcobatus* - Black Greaseweed** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Selenium - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Senecio* - Ragwort - Groundsel** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Senna, Coffee Senna - *Cassia* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Sesbania* spp.** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Silverstone - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Skeletal Muscle Relaxants and Aminoglycoside Antibiotics - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Slaframine - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Sleepy Grass - *Stipa Robusta* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Smoke Inhalation - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Snakes, North American Poisonous - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Sneezeweeds - *Helenium* spp. - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Solanaceae, Solanine, Solandine, and Solanocapsine, Introduction to - Search in *Veterinary*

Toxicology - *All relevant IVIS chapters*
***Solanum* spp - Nightshade group** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Sophora* - Mescal beans** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Sorghum* spp - Hybrid Sudan** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Spring Parsley - *Cymopterus* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Spurge Laurel, Daphne - Mezereon - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Spurges - *Euphorbia* spp. - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
St. Johnswort - *Hypericum* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Staggers Syndromes - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Stipa Robusta* - Sleepy Grass** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Strychnine - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Sulfonamides - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Sumpweed - *Iva Augustifolia* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Sweet Clover Hay - Damaged or Moldy - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

T

Tall Fescue - *Festuca Arundinacea* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Tannic Acid - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Taxus* - Yew** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Teflon - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Teratogenic Agents - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Testicular Degeneration, Toxic Agents that Cause - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Tetanus - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Tetradymia* - Artemisia Poisoning** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Thallium - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Thiacetarsemide Sodium (Caparsolate) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Thiaminase and Thiamine (Vitamin B1) Deficiency - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Tick Paralysis - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toad Poisoning - *Bufo* Toxicosis - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Tobacco - *Nicotiana* spp. - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxic Agents that Cause Testicular Degeneration - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxic Gases Overview - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicants that Affect Neurotransmitters - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicology of the Cardiovascular System, Introduction to the - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicology of the Erythrocytes, Platelets, and Clotting Proteins, Introduction to the - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicology of the Liver, Introduction to the - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicology of the Urinary System - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicology, Introduction to - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Toxicosis, Diagnosis and Management of - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Tremorgenic Mycotoxins and Various Staggers Syndromes - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Tribulus* - Puncture Vine** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Trichothecene Mycotoxins - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Tricyclic Antidepressants - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Trifolium* (Clovers) and *Medicago* (Alfalfa and Medics)** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Turpentine - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

U

Urinary System, Toxicology of the - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

V

Vacor - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

Veratrum - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Vetchlings - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Vicia Villosa* - Hairy Vetch** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Viscum* and *Phoradendron* spp. - Mistletoe** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Vitamin D - Containing Plants - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Vitamin K and Coagulation of the Blood - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Vitamin K3 (Menadione) - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

W

Water Deprivation - Sodium Ion Toxicosis - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Water Hemlocks - *Cicuta* spp - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
White Snakeroot - *Eupatorium Rugosum* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Wild Barley - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

X

***Xanthium* spp. - Cocklebur** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

Y

Yellow Star Thistle and Russian Napweed - *Centauria* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Yew - *Taxus* - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

Z

Zearalenone and Zearalenol - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
***Zigadenus* - Death Camas** - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Zinc - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*
Zinc Phosphide and Aluminum Phosphide - Search in *Veterinary Toxicology* - *All relevant IVIS chapters*

Annotated Tables of Toxicants

Section II: Toxicants that Affect the Nervous System

Toxicants Associated with Seizures

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Annotated Table of Toxicants Associated with Seizures]

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Strychnine (Indole alkaloid-containing agent)	All, esp.dogs	Minutes to Hours	Hours to few days
***Calycanthus* - Bubby Bush** (Indole alkaloid-containing agent)	Herbivores, esp. cattle	Minutes to Hours	Few days; often lethal
***Gelsemium* - Yellow or Carolina Jessamine** (Indole alkaloid-containing agent)	Herbivores, fowl	Minutes to several days	Few days; often lethal
Tetanus	All species, esp. horses	Days to weeks	Days to months; potentially lethal
Metaldehyde	All species, esp. dogs	• Minutes to hours (neurologic or respiratory effects). • Days (liver failure).	• One to two days; often lethal • Days to months; liver failure rare.
Fluoroacetate-1080	All species, esp. carnivores, rodents (target species)	Hours	Few days; often lethal
5-Fluorouracil	All, esp.dogs	Minutes to Hours	Weeks often lethal
Castrix (crimidine) (rodenticide)	All species	Minutes	Hours; potentially lethal
Acute Fluoride Toxicosis	See Toxicants that Affect the Teeth and Skeletal System		
Japanese Yew (*Taxus*) in dogs	See Toxicants that Affect the Heart		

Toxicants Associated with Stimulation or Seizures

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Annotated Table of Toxicants Associated with Stimulation or Seizures

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Diphenyl Aliphatic and Miscellaneous Organochlorine Insecticides (Organochlorine insecticides)	All Species	Minutes to chronic	Hours to days; often lethal
Cyclodiene Organochlorine Insecticides and Lindane (Organochlorine insecticides)	All species	Minutes to chronic	Hours to days; often lethal
4-Aminopyridine (Avicide)	All species, especially target birds	Minutes	Hours; potentially lethal
Chocolate, Caffeine, and other Methylxanthines	All species, esp. smaller dogs	Minutes to hours	Hours; potentially lethal
Nitrofuran Toxicosis (Nitrofurans)	All species, esp. cattle, poultry	Hours to weeks	Days; often lethal
Dicentra cucullaria - Dutchman's Breeches and other *Dicentra* spp.	Herbivores	Minutes to hours	Minutes to hours; poisoning is rare
4-Methyl-Imidazole (ammoniated foodstuffs)	Herbivores, esp. ruminants	Minutes to days	Hours to days; often lethal
Water Deprivation - Sodium Ion Toxicosis	All species, esp. swine, cattle, poultry	Minutes to days	Hours to days; often lethal Permanent brain damage possible
Amphetamine Toxicosis	Small animals, horses	Minutes	Hours to a day or so; potentially lethal
Cocaine Toxicosis	Small animals	Minutes to hours	Hours; potentially lethal
Tremorgenic Mycotoxins and Various Staggers Syndromes includes penitrem, roquefortine, ryegrass staggers (lolitrem B), Dallis grass staggers (paspalitrems), and possibly Bermuda grass staggers	All species, esp. dogs, cattle	Minutes to days	One day to weeks; often lethal in dogs
Zinc phosphide (rodenticide)	All species, esp. dogs	Minutes to hours (neurologic or respiratory effects). Days (liver failure)	Neurologic signs: 1 to 2 days; often lethal Liver damage: days to permanent
Aluminum phosphide (Fumigant)	All species	Minutes to hours (neurologic or respiratory effects). Days (liver failure)	Neurologic signs: 1 to 2 days; often lethal Liver damage: days to permanent
***Cicuta* spp. - Water Hemlocks**	Herbivores, esp. ruminants, swine	Minutes	Hours; often lethal

***Corydalis caseana* - Fitweed**	Herbivores, esp. sheep	Minutes	Hours to 2 days; potentially lethal
Milkweeds (*Asclepias*)	Herbivores, esp. sheep	Minutes to hours	Hours to days; potentially lethal
***Oligomeris* - Desert Spike**	Cattle	Days to weeks	Unknown; potentially lethal

Toxicants with Mixed Effects on the Central Nervous System

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Annotated Table of Toxicants with Mixed Effects on the Central Nervous System

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Lead Toxicosis	Most species, especially dogs, horses, cattle, waterfowl. Swine resistant.	Hours to months	Days to permanent damage; often lethal
Mercury	All species, especially swine, cats	Hours to weeks	Days to permanent damage; poisoning in domestic animals is rare, but poisoned animals often die
Organotin Compounds - trialkyl tin compounds (fungicides, wood preservatives, algicides, paints)	All species	Hours to weeks	Days to permanent damage; potentially lethal
Quaternary ammonium disinfectants (ingested)	Dogs	Minutes to hours	Hours; potentially lethal
Ammonia toxicoses (urea and other sources of nonprotein nitrogen)	Herbivores, especially ruminants	Minutes to hours	Hours; often lethal
Pyrethrum (Pyrethrins) and Pyrethroids (insecticides)	Cats, dogs	Minutes to hours	Hours (usually) to two days; rarely lethal
Rotenone	Cats, dogs, birds, fish, amphibians	Minutes to hours	Hours to days; infrequently lethal except in aquatic organisms and arthropods
Tricyclic Antidepressants	Dogs, cats	Minutes to hours	Days; often lethal
Fumonisins (mycotoxins)	Horses, and possibly rabbits may have neurologic effects	Several days to months	Permanent damage likely in horses that survive; often lethal
Centauria - Yellow Star Thistle and Russian Napweed Cause of "Chewing Disease" of Horses (*Centauria solstitialis* and *Centauria repens*)	Horses	Days to months	Permanent damage often lethal

Thiaminase-Containing Plants and Other Substances

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Annotated Table of Thiaminase-Containing Plants and Other Substances

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
***Pteridium Aquilinum* (Also Called *Pteris Aquilina*) - Bracken Fern** (in monogastrics)	Horses	Weeks to months	Weeks to permanent damage; potentially lethal
***Equisetum Arvense* - Horsetail**	Horses	Weeks to months	Weeks to permanent damage; potentially lethal
Thiaminase and Thiamine (Vitamin B_1) Deficiency in Cats, Dogs, **Fur-Bearing and Marine Mammal Species** (Uncooked fish)	Cats, dogs, foxes, mink, captive marine mammals	Weeks	Days to permanent damage; potentially lethal
Kochia (high in sulfate) (thiamine-responsive polioencephalomacia) Other sources os sulfate, such as high sulfate water and gypsum (when fed) have been linked epidemiologically with thiamine-responsive polioencephalophalomacia. For diagnosis, it is of value to quantify dietary and water sulfur intake; and blood thiamine. [See the complete list of references]	Cattle	Weeks to months	Weeks to permanent damage; often lethal

Toxicants that Cause Central Nervous System Depression

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Annotated Table of Toxicants that Cause Central Nervous System Depression

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
***Eupatorium rugosum* - White Snakeroot**	Cattle, horses, sheep, goats	Days to weeks	10 - 14 days in cattle; permanent heart damage in horses; often lethal in both species
***Isocoma wrightii* - Previously *Haplopappus* or *Aplopappus* - Rayless Goldenrod**	Herbivores, esp. goats	Days to weeks	Days to weeks; potentially lethal especially in goats
Opiates and Opioids	Dogs, cats	Minutes to hours	Hours to 2 days
***Cannabis sativa* - Marijuana** (hemp)	Dogs, rarely cats	Minutes to hours	One to 2 days; unlikely to be lethal
Ivermectin and Milbemycin	Dogs (esp. Collies), cats, foals	Hours to a day	Days to weeks; potentially lethal
Amitraz	Dogs, horses, cattle	One hour to 2 days	1 - 3 days; may be lethal to swine, horses, young puppies
Benzyl Alcohol and Benzoic Acid	Cats; neonates of all species	Hours to days with multiple doses	Up to a few days, potentially lethal
Citrus Oil Extracts	Cats, dogs	Minutes to hours	Hours to 1 day; unlikely to be lethal
***Stipa robusta* - Sleepy Grass**	Horses	Days	Up to 2 days; unlikely to be lethal
Piperazine	Cats, dogs	Within 24 hours	1 - 3 days; rarely lethal
Bendodiazepines (e.g. diazepam)	Dogs, cats	1 - 4 hours	Hours to 3 days; rarely lethal in dogs, potentially lethal hepatoxicity in cats (after 1 week of administration)
Barbiturates Ingestion by carnivores and scavengers [e.g. dogs, foxes, coyotes, raptors, etc.] of pentobarbital or other euthanasia drugs in recently euthanatized animals (generally livestock) can result in severe, potentially lethal (esp. in raptors) toxicosis	All species	Minutes to hours	Hours to a few days; potentially lethal
Tranquilizers	All species	Minutes	Hours potentially lethal after intra-arterial injection
Phenothiazine tranquilizers	All animals	Minutes to hours	Hours to 2 days; infrequently lethal
Isopropanol	Cats, dogs	Minutes	Hours to 1 day; potentially lethal

Ethanol Ethanol toxicosis occurs occasionally in cage birds, dogs, an cats from alcoholic beverages, dogs that ingest bread dough (causes ethanol toxicosis and/or severe digestivetract distention due to "rising" of the dough *in vivo*), silage-feed or stillage-fed cattle (also brewer's grains), and cedar waxwings that gorge on fruits that have fermented alcohol late in the season.	All species	Minutes	Up to 3 days
Methylene chloride and other hydrocarbon solvents	All species	Minutes to hours	Hours to 3 days; lethality varies among compounds

Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)

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Annotated Table of Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Nondepolarizing Cholinergic Blockers			
Tertiary amines (no charge, cross the blood-brain barrier)			
Atropine (D, L hyoscyamine)	Cattle, dogs, cats, and esp. horses	Minutes	Hours to a day in small animals, horses (up to 3 days); up to several days in cattle; potentially lethal, esp. in horses
Scopolamine (L-hyoscine)	Effects similar to atropine; toxicosis unlikely when used at recommended doses		
Benztropine (Cogentine ®)	Effects similar to atropine; toxicosis unlikely when used at recommended doses		
Aminopentamide (Centrine ®)	Effects similar to atropine; toxicosis unlikely when used at recommended doses		
Quaternary amines (charged compounds, do not cross the blood-brain barrier; CNS signs unlikely)			
Atropine methyl nitrate	Toxicosis unlikely when used at recommended doses		
Scopolamine methyl bromide	Toxicosis unlikely when used at recommended doses		
Homatropine methyl bromide	Toxicosis unlikely when used at recommended doses		
Propantheline (Pro-Banthine ®)	Toxicosis unlikely when used at recommended doses		
Glycopyrrolate (Robinul-V ®)	Toxicosis unlikely when used at recommended doses		
Plants of the Solanaceae that consistently cause cholinergic blockade at muscarinic receptors (i.e. a atropine-like effects)			
Atropa belladonna - Belladonna Plant	Cattle, horses, and esp. swine	Minutes to hours	Hours to 3 days, poisoning is rare
Henbane (*Hyoscyamus niger*)	Poultry, cattle, sheep	Minutes to hours	Hours to 3 days
***Datura stramonium* - Jimson Weed**	Horses, cattle, sheep, swine, chickens, ostriches	Minutes to hours	Hours to 3 days
Mushrooms			
Anticholinergic Mushrooms (*Amanita panterinae*, most members of the species, *A. muscaria*), and other species	Mostly small animals	Minutes to hours	Hours, rarely lethal
Plants of the Solanacae that usually cause cholinergic blockade (at muscarinic receptors), but which in other cases [1] may contain solanine solanidine and thus cause gastrointestinal upset and CNS disturbances.			
***Physalis* spp. - Ground Cherry (Members of the Solanaceae)**	All species	Minutes to hours	Hours to 3 days
Matrimony Vine (*Lycium halimifolium*)	All species	Minutes to hours	Hours to 3 days
***Cestrum* spp. - Jessamines**	Pet animals	Minutes to	Hours to 3 days

(some Cestrum diurnum plants contain toxic amounts of vitamin D)		hours	
Potato (*Solanum tuberosum*)	Herbivores	Minutes to hours	Hours to 3 days
Plants of the Solanacae that sometimes cause cholinergic blockade (at muscarinic receptors), but which more often may contain toxic amounts of solanine and solanidine and thus gastrointestinal upset and CNS disturbances. [1]			
Black nightshade (*Solanum nigrum*)	Herbivores	Minutes to hours	Hours to 3 days
Jerusalem cherry (*Solanum pseudocapsicum*) (may also contain cardiotoxic solanocapsine)	Herbivores	Minutes to hours	Hours to 3 days
Tomato leaves, green fruit (*Lycopersicon*) (may also contain toxic amounts of nitrate)	Herbivores	Minutes to hours	Hours to 3 days; may also contain nitrate
[1] Note: In contrast to the effects of atropine, the clinical effects of the other major solanaceous alkaloids (solanine, solanidine, etc.) which predominate in many of the Solanaceae are due largely to gastrointestinal irritation and central nervous system effects.			
Muscarinic Agonists			
Pilocarpine	All species	Minutes	Hours; rarely lethal
Arecoline (obsolete drug formerly used to treat small animals for tapeworms)	Dogs, cats	Minutes	Hours; rarely lethal
Methacholine	All species	Minutes	Hours; rarely lethal
Carbachol	All species	Minutes	Hours; rarely lethal
Bethanechol	All species	Minutes	Hours; rarely lethal
Muscarinic - Histaminic Mushrooms e.g.: - *Clitocybe dealbata* - *Inocybe* spp. - *Amanita muscaria* (only a minority of members of the species contain toxic amounts of muscarine) - *Boletus* - Others	Mostly pet animals	30 minutes to hours	Hours to 2 days; rarely lethal
Slaframine Mycotoxin in legume forages. Most often in red clover (*Trifolium pratense*) infected with the fungus *Rhizoctonia leguminicola*	Cattle, horses, sheep	Hours	Up to 3 days; unlikely to be lethal
Inhibitors of Cholinesterase (secondary effect is stiumulation of cholinergic receptors by excessive acetylcholine)			
Organophosphorus insecticides and avicides	All species	Minutes to hours	Days to 4 weeks; often lethal
Carbamate insecticides	All species	Minutes to hours	Hours to 1 day; often lethal
***Anabaena flos-aquae* - Blue-Green Algae** [Anatoxin-a(s)]	All species	Minutes to hours	Days; often lethal
Solanine and solanidine-containing plants (some of the Solanacae)	All species	The significance of cholinesterase inhibition is not clearly established in clinical toxicoses	
Nicotinic Agonists (compounds that stimulate nicotinic cholinergic receptors)			
Blue-Green Algae (*Anabaena* or *Oscillatoria)* (Anatoxin-a)	All species	Minutes to hours	Several hours to days; often lethal
Nicotine	All species, esp.	Minutes to	Hours; often lethal

(Blackleaf 40 ®), (Cap-Chur-Sol ®) nicotine patches	dogs and other small companion animals	2 hours	
***Nicotiana* spp. - Tobacco**	Herbivores, swine, dogs, birds	Minutes to hours	Hours; potentially lethal; teratogenic
Indian Tobacco (*Lobelia*)	Sheep, cattle, goats	Minutes to hours	Days to weeks; potentially lethal
Cardinal flower (*Lobelia*)	Sheep, cattle, goats	Minutes to hours	Days to weeks; potentially lethal
Giant lobelia (*Lobelia*)	Sheep, cattle, goats	Minutes to hours	Days to weeks; potentially lethal
***Conium* - Poison Hemlock** (*Conium maculatum*)	Cattle, swine, poultry, horses, sheep	Minutes to hours	Hours; potentially lethal; teratogenic
***Lupinus* - Lupine or Bluebonnet**	Sheep, cattle, and other herbivores	1 - 24 hours	Hours to days; potentially lethal; teratogenic
***Sophora* - Mescal Beans**	(See Toxicants with Mixed Effects on the Central Nervous System)		
***Gymnocladus dioica* - Kentucky Coffee Tree**	Sheep, cattle, horses	1 to a few hours	Hours to days; potentially lethal
***Laburnum anagyroides* - Golden Chain**	Herbivores	Within a few hours	Hours to 2 days; potentially lethal
Levamisole	Horses, cattle, sheep, swine, dogs, marine mammals	Minutes to a few hours	Unlikely to be lethal
Imidacloprid	Small animals?	Minutes to hours	Unlikely to be lethal
Nicotinic antagonists			
Succinylcholine	All species	Minutes	Minutes; potentially lethal

Toxicants that Cause Paresis or Paralysis

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Annotated Table of Toxicants that Cause Paresis or Paralysis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Any cholinesterase inhibitor	(See Inhibitors of Cholinesterase)		
Any nicotinic agents	(See Toxicants with Nicotinic Effects)		
Black Widow Spider (*Latrodectus* spp.)	All species	Within 6 hours	Hours; infrequently lethal
Neuromuscular Blocking Agents	All species	Minutes	2 - 4 hours; potentially lethal
***Delphinium* - Larkspur**	Mostly cattle	1 - 4 hours	Often rapidly lethal
Botulism	Most species; especially waterfowl	12 - 48 hours	Days to months; often lethal
Tick Paralysis (*Dermacentor*, *Amblyoma* and some species of *Ixodes*)	Cattle, sheep, dogs, cats, deer, llamas	3 - 9 days	Days sometimes lethal
Phenylarsonics	Swine, poultry	Days	Weeks to permanent damage (common); potentially lethal
Organophosphorus-Induced Delayed Neuropathy (OPIDN) that cause organophosphorus-induced delayed neuropathy [OPIDN]; not all are insecticides, e.g.: - Tri-irtho-crestyl phosphate (TOCP) - EPN (insecticide) - Haloxon (anthelmintic) - Chlorpyrifos (massive doses in domestic cats)	Cattle, swine, cats, chickens	2 - 4 weeks	Weeks to permanent (common)
***Lathyrus* spp. - Vetchlings** (Lathyrism, rough pea, vetchlings)	Horses, cattle	10 days to 2 months	Weeks to permanent damage
***Sorghum* spp. - Hybrid Sudan (Equine Cystitis-ataxia and Teratogenesis Syndromes)**	Horses	Average 8 weeks	Often permanent neurologic damage; secondary urinary tract infection may be lethal; also teratogen in horses
***Acacia* spp.** Guajillo (*Acacia berlandieri*)	Sheep, goats	6 - 9 months	Months; may be lethal; up to 50% may die
***Karwinskia humboldtiana* - Coyotillo**	Cattle, sheep, goats, horses	Weeks to months	Weeks to permanent damage
Citreoviridin (Mycotoxin)	Cattle	(Importance of this mycotoxin in the field has not been well established)	
Patulin (Mycotoxin)	Cattle	(Toxicosis is very rare)	
Avidin			

in raw egg white (causes biotin deficiency), however, egg yolks are rich in biotin			
Locoweed (*Astragalus* and *Oxytopis*) (Miserotoxin = 3-nitro compounds)	(See Toxicants with Mixed Effects on the Central Nervous System)		
Solanum dimidiatum	Cattle	Unknown	Chronic to permanent damage; potentially lethal
Cycad palms (*Cycas* or *Zamia*)	Herbivores, dogs, swine	Hours to a few days	Weeks to permanent damage; often lethal
Lolitrem B from *Acremonium lolii* in perennial ryegrass (*Lolium perenne*)	Sheep, cattle, sometimes horses	Chronic	Chronic; rarely lethal
Tetrodotoxin (sodium channel blocker) in: - Puffer fish (*Tetraodon* and *Fugu*) - California newt (*Taricha*; a salamander) - European newt (*Tariturus*; a salamander) - Unk (*Bombia*; a salamander)	Pet animals (carnivores)	Minutes to hours	Days to several weeks
Saxitoxin and neosaxitoxin (sodium channel blockers). Responsible for paralytic shellfish poisoning-from cocles, mussels, clams. Name derived from the Alaskam butter clam, *Saxidomas giganticus*). Poisoning is much more commonly a result of eating oysters. All acquire the toxin from the dinoflagellate, *Gonyaulax* spp., usually evident as "red tides". The same toxins are produced by certain strains of at least 2 species of blue-green algae (*Aphanizomenon flos-aquae* and *Anabaena flos-aquae*)	Pet animals (from eating shellfish); All species (from drinking blue-green algae in surface waters)	Minutes to hours	Hours to months. Human cases often reported; potentially lethal
Ciguatera (ichthyosarcotoxin, that causes sodium channels to stay open) in red snapper, barracuda, and other warm water, carnivorous, marine fish that bioaccumulate the toxin synthesized by marine benthic dinoflagellates, e.g., *Gambierdiscus* spp. Ciguatera causes neurologic, gastrointestinal, and cardiac dysfunction.	Pet animals	Hours to two days	Days to weeks; rarely lethal
Sulfonamides (cause peripheral neuritis)	All species esp. chickens and cattle	Days to weeks	Weeks to permanent damage; potentially lethal
Mephenesin	Small animals	Hours to days	Hours to days; unlikely to be lethal
Selenium (*Lycopersicon*) (may also contain toxic amounts of nitrate)	Swine; other species	Seven weeks to months	Damage may be permanent; potentially lethal

Toxicants that Primarily Cause Respiratory Paralysis

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Annotated Table of Toxicants that Primarily Cause Respiratory Paralysis

See Toxicants that Cause Paralysis, Inhibitors of Cholinesterase, Nicotinic Agonists; and Primary Muscle Dysfunction and/or Paralysis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Hydrogen Sulfide (H_2S)	Swine, all species	Minutes to 2 hours	Few hours, generally animals in confinement are affected; rapid death occurs; major hazard to farm workers
Aminoglycoside Antibiotics and Skeletal Muscle Relaxants	All species	Minutes to hours	Hours to 2 days; may be lethal

Toxicants that Cause Primary Muscle Dysfunction and/or Paralysis

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Annotated Table of Toxicants that Cause Primary Muscle Dysfunction and/or Paralysis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Phenoxy Herbicides (2,4-D, MCPP, Silvex, 2,4,5-T, and Others)	Dogs, hervbivores	Within 24 hours	Days; rarely lethal
Monensin (Rumensin ®, Coban ®) (Ionophores*)	Horses, ruminants, poultry	Hours to days	Few days to permanent damage; cardiac involvement frequent in horses; often lethal
Lasalocid (Bovatec ®) (Ionophores*)	Dogs, horses	Hours to days	Days to permanent damage; potentially lethal
Salinomycin (Ionophores*)	Horses, cats	Hours to days	Days to permanent damage; potentially lethal
Laidlomycin priopiopinate (Ionophores*)	Horses	Hours to days	Days to permanent damage; potentially lethal
Narasin (Ionophores*)	Horses	Hours to days	Days to permanent damage; potentially lethal
* **Ionophores**: (See Toxicants that Affect the Heart, Organic Compounds)			
Senna (*Cassia*) (See Toxicants that Affect the Heart)	Herbivores, poultry	Days to weeks	Weeks to permanent damage; potentially lethal
Hairy vetch (*Vicia villosa*) (See Toxicants that Affect the Skin)	Herbivores, esp. black cattle	Days to months	Weeks to permanent damage; potentially lethal
Lathyrus (vetchlings)	(See Toxicants that Cause Paralysis)		
Avocado (*Persea americana*) [See Galey F. In: Colgate SM and Dorling PR (eds.) Plant Associated Toxins: Agricultural, Phytochemical and Ecological Aspects. CABI Publishing 1997. - Available from amazon.com -]	(See Toxicants with Mixed Effects on the Central Nervous System)		
Thermopsis montana	Cattle	Weeks to months	Months to permanent damage; potentially lethal
Vitamin D-containg plants e.g. *Cestrum Diurnum* and *Solanum malacoxylon*	(See Nephrotoxic Plants)		

Toxicants that Cause Acidosis

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Annotated Table of Toxicants that Cause Acidosis			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Ethylene Glycol	All species; esp. dogs, cats	30 min to a day	Days; often lethal
Methanol	Mostly pet animals	Minutes to hours	Few hours to 2 days; potentially lethal
Aspirin and Salicylates	Cats, dogs	Minutes to chronic	Days; potentially lethal
d,l-Methionine	(See Toxicants with Mixed Effects on the Central Nervous System)		
Phenolics	(See Hepatotoxic Drugs and Chemicals)		
Any shock-inducing syndrome (metabolic acidosis)	-	-	-
Any syndrome with prolonged exertion or seizures (metabolic acidosis)	-	-	-
Any Syndrome with severe pulmonary failure or respiratory paralysis (respiratory acidosis)	-	-	-
Other agents that cause acidosis			

Toxicants that Cause Fevers

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Annotated Table of Toxicants that Cause Fevers

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Pentachlorophenol (wood preservative) (Uncoupler of oxidative phosphorylation)	Most species	Hours	Days for most compounds; often lethal
Disophenol (DNP, an obsolete anthelminic) (Uncoupler of oxidative phosphorylation)	Most species	Hours	Days for most compounds; often lethal
Dinitrophenol and Other Uncouplers of Oxidative Phosphorylation (Uncoupler of Oxidative Phosphorylation)	Most species	Hours	Days for most compounds; often lethal
Aspirin (See Toxicants that Cause Acidosis)	Most species	Hours	Days for most compounds; often lethal
Bromethalin (See Toxicants Associated with Mixed Effects on the CNS)	Most species	Hours	Days for most compounds; often lethal
Hexachlorophene (See Toxicants Associated with Mixed Effects on the CNS)	Most species	Hours	Days for most compounds; often lethal
Halothane	Swine, dogs (esp. greyhounds)	Minutes to hours	Hours; often lethal
Garbage toxicosis	(See Bacterial Toxins that Affect the GI Tract)		
Any Syndrome with seizures or exertion	(See Toxicants Associated with Stimulation or Seizures)		

Section VI: Toxicants that Affect the Kidneys

Nephrotoxic Metals and Inorganics (Last Updated: 9-Aug-1999)

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Annotated Table of Nephrotoxic Metals and Inorganics

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Cadmium	Most species	Days to weeks	Weeks to permanent damage; potentially lethal; toxicosis is rare
Zinc [metallic objects (zinc nuts or esp. pennies) and galvanized metal]	Dogs, seals, caged birds, ostriches	Days	Days to permanent damage; often lethal
Boric Acid and Borate (insecticides)	Mostly pets	Hours to days	Days to weeks; toxicosis rare; deaths very rare
Calcium	Poultry (nonlayers)	Chronic	Chronic; often lethal
Mercury	(See Toxicants with Mixed Effects on the Nervous System)		
Copper	(See Toxicants that Cause Hemolysis)		
Phosphorus	(See Toxicants that Affect the Liver)		
Uranium	(Toxicosis is rare)		
Bismuth	(Toxicosis is rare)		
Chromium	(Toxicosis is rare)		

Nephrotoxic Organic Compounds

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Annotated Table of Nephrotoxic Organic Compounds

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Vitamin K3 (injectable Menadione ®; no longer marketed)	Horses	5 - 48 hours	5 - 7 days; often lethal
Blister Beetle - Cantharidin Toxicosis (*Epicauta* spp.)	Horses, cattle, sheep	Hours	Few days; often lethal
Sulfonamides	Most species, esp. carnivores, poultry	Days to weeks	Days to permanent damage; potentially lethal
Amphotericin-B	Most species	Days to weeks	Few days to permanent damage; potentially lethal
Other Nephrotoxic Antibacterial Agents Nephrotoxic antibiotics, e.g.: - Oxytetracycline - Bacitracin - Polymyxin-B - Gentamycin - Neomycin - Cephalosporins	Most species	Days to weeks	Days to permanent damage; potentially lethal
Carbamate Fungicides	-	-	-
Non-steroidal anti-inflammatory drugs See Nonsteroidal Anti-Inflammatory Agents	Small animals, horses	Hours to days	Days to permanent damage; often lethal
Ethylene glycol	(See Toxicants that Cause Acidosis)		
Oxalic acid (rust remover)	Mostly dogs	Minutes to hours	Few days to permanent damage; often lethal but toxicosis is rare
Vitamin D3 (especially cholecalciferol rodenticides)	Dogs, other pet animals	24 - 72 hours	Weeks to permanent damage; often lethal
Stillage liquid from ethanol production	Cattle	(Syndrome not yet confirmed)	-
Carbon tetrachloride	(See Hepatotoxic Chemicals and Drugs)		
Phenolics	(See Hepatotoxic Chemicals and Drugs)		
Carp gallbladders (ingestion, from any of several species of carp; uncooked)	-	-	-
Diquat (Herbicide)	Most species	Few days	Days to weeks; potentially lethal

Nephrotoxic Plants

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Annotated Table of Nephrotoxic Plants

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Vitamin D - Containing Plants (*Cestrum diurnum*, *Solanum malacoxylon*)	Cattle, horses, sheep, swine	Weeks to months	Months to permanent damage; potentially lethal
Beets (*Beta*) (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
Curly dock (*Rumex*) (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
Lamb's quarters (*Chenopodium*) (Soluble oxalate-containing plant) (See Miscellanous Plants that Affect the GI Tract)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
- Kochia Scorpia (Soluble oxalate-containing plant) (See Poisonous Plants that Affect the Liver)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
Rheum - Rhubarb (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
Halogeton (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
***Sarcobatus* - Black Greaseweed** (Soluble oxalate-containing plant)	Herbivores	Few hours to weeks	Weeks to permanent damage; potentially lethal to often lethal
***Amaranthus* spp. - Pigweed** (*Amaranthus retroflexus*)	Swine, cattle	Days to weeks	Weeks to permanent damage; may be lethal
***Quercus* - Oak** (acorns)	Esp. ruminants	Days to weeks	Weeks to permanent damage; may be lethal
***Lilium* and *Hemerocallis* spp.** (Lily and day Lily)	Cats	0.5 - 3 days	Days to permanent damage; often lethal
Hybrid Sudan or Sudan Grass (*Sorghum* spp.) [Indirect effect of equine cystitis - ataxia syndrome (ascending infections)]	(See Toxicants that Cause Paralysis)		
Cocklebur (Xanthium)	(See Poisonous Plants that Affect the Liver)		

Nephrotoxic Mycotoxins

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Annotated Table of Nephrotoxic Mycotoxins

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Ochratoxins	Swine, poultry	Days to weeks	Days to permanent damage; often lethal in poultry
Citrinin	(may coexist with, and potentiate the effect of, ochratoxins)		
Fumonisins	Rabbits, and probably sheep (rats and mice also susceptible to fumonisin-induced renal damage)	Days to weeks	Weeks to permanent damage; potentially lethal

Toxicants that Cause Goiter

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Annotated Table of Toxicants that Cause Goiter

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Iodine	Horses	Chronic	Months
Soybean (*Glycine*) (rare)	-	-	-
Flax linseed (*Linum*)	(See Toxicants that Inhibit the Function of Respiratory Pigments)		
Castor bean (*Ricinus*)	[See Plants that Affect the Gastrointestinal Tract, Lectins (Toxalbumins)]		
Sulfonamides	(See Toxicants that Affect the Kidney)		
***Brassica* and Related Genera, *Brassica* spp.** (Cabbage, broccoli, kale, rape)	Horses	Chronic	Months

Teratogenic Agents

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Annotated Table of Teratogenic Agents

Specific Agents	Major Species	Usual Effects
Note - For most teratogens, the time of greatest effect is the first trimester. Individual chapters should be examined to determine the critical times of exposure in susceptible species.		
Veratrum (False hellebore - *Veratrum califronicum*)	Sheep, cattle	In sheep: causes "monkey face", cyclops, anophtalmia, cleft palate; shortened maxilla, arthrogryposis, shortened long bones
Tobacco (*Nicotiana*) (Plant with nicotinic as well as teratogenic alkaloids)	Swine, cattle	Arthrogryposis, spinal curvature, torticollis
Poison hemlock (*Conium*) (Plant with nicotinic as well as teratogenic alkaloids)	Swine, cattle	Arthrogryposis, other skeletal malformations, cleft palate
Lupine, bluebonnet (*Lupinus*) (Plant with nicotinic as well as teratogenic alkaloids)	Cattle, sheep	Arthrogryposis, other skeletal malformations, cleft palate
Locoweed (*Astragalus* and *Oxytropis*)	Herbivores, sheep	Arthrogryposis, or contracted tendons
Hybrid Sudan or Sudan grass (*Sorghum*)	Herbivores	Ankylosis, contracted tendons
Lathyrism (*Lathyrus* spp.)	Herbivores	Various skeletal deformities
Potato (*Solanum tuberosum*)	Hamster	Spina bifida, exencephaly
Fescue (*Festuca* with ergot alkaloids produced by the endophytic fungus *Acremonium coenophialum*)	Horses	Dystocia with thick placenta, and oversize, weak foals with overgrown hooves
Mercury	All species, especially cats	Hypoplasia of the cerebellum and other brain defects
Organotins	Wildlife in aquatic ecosystems	Skeletal malformations, defective myelinogenesis
Selenium	Poultry, waterfowl	Hypoplasia of upper and/or lower beak, hindlimbs, wings, and eyes
Halogenated dibenzodioxins and related halogenated aromatics	Laboratory animals, predatory water birds	Cystic kidneys, cleft palate. Crossed beaks in cormorants
Vitamin A and derivatives such as isotretinoins	Humans, swine, rabbits, other species	Shortened limbs, altered gait, spinal column abnormalities, cleft palate, malformed ears, craniofacial bone and brain anomalies, microphtalmia
Corticosteroids	Dogs, possibly other species	Cleft palate
Griseofluvin	Cats	Cyclops

Thalidomide	Human beings, lab rodents	Hypoplasia of the limbs (phocomelia)
Cocaine	Human beings	Severe neurologic impairment
Ethanol	Human beings	Shortened palpebral fissures (eye opening is small relative to the globe) and ocular problems, premaxillary abnormalities resulting in a flattened midface and an indistinct philtrum. Low birth weght, learning impairment, mental retardation, and microencephaly. Hearing impairment and ears rotating posteriorly. Gait abnormalities, scoliosis, shortened digits. Atrioventricular septal defects. Renal disorders. Threshold dose is only 1 ounce of alcohol/day (causes reduced birth weight). Overall, 5.9% of human newborn babies are affected by some degree of fetal alcohol syndrome.
Other teratogens	-	

Abortion Inducing Toxicants

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Annotated Table of Abortion Inducing Toxicants
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Specific Agents	Major Species	Usual Time of Abortion	Usual Duration (if survives)
***Pinus* - Pines** (Western yellow pine, ponderosa pine)	Cattle, sheep	Less than 2 days to 2 weeks after initial exposure	Single feeding may cause abortion
Broomweed (*Gutierrezia Microcephala* = *Xanthocephalum* spp.)	Cattle, swine	After 7 to 117 days of feeding	Abortion of weak and small young
***Cupressus Macrocarpa* - Monterey Cypress**	Cattle	2 - 8 weeks before term	Premature births, stillbirth
***Iva augustifolia* - Sumpweed**	Cattle	Third trimester	Abortion; possible early mammary gland development
Subterranean clover (*Trifolium subterranean*) (See Estrogenic Toxicants)	Cattle	Third trimester	Abortion; possible early mammary gland development
Locoweed (*Astragalus*)	(See Toxicants that Cause Mixed Effects on the CNS)		
Lupine (*Lupinus*)	(See Toxicants with Nicotinic Effects)		
Hybrid Sudan (*Sorghum* spp.)	(See Toxicants that Cause Paralysis, and Methemoglobin Producers)		
Lead	(See Toxicants with Mixed Effects on the Central Nervous System)		
Nitrate	(See Methemoglobin Producers)		
Carbon Monoxide	(See Toxicants that Inhibit the Function of Respiratory Pigments)		
Corticosteroids	-		
Phenothiazine	(See Toxicants that Cause Skin Damage by Primary Photosensitization)		
Halogenated dioxins and related compounds; includes highly chlorinated naphtalene	(See Other Organic Compounds)		
Vitamin A-D injectable	-		
Vitamin E and Selenium (MuSe)			

Estrogenic and Anti-androgenic Toxicants

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Annotated Table of Estrogenic and Anti-androgenic Toxicants			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Estrogenic Compounds			
Zearalenone and Zearalenol	Swine, cattle, sheep	Days to weeks	Days to weeks, permanent reproductive damage rare
***Trifolium* (Clovers) and *Medicago* (Alfalfa and Medics)** (Subterranean and other clovers)	Sheep and possible cattle	Chronic	With prolonged exposure, can have permanent infertility
Diethylstillbesterol (**DES**) (no longer available)	All species	Hours to days	Once used in dogs for mismating and urinary incontinence. Transplacental carcinogen in women exposed *in utero*
ECP (**estradiol cypionate**)	Dogs	Hours to days	Weeks to months; potentially lethal
Wheat germ	-	-	-
Soybean (*Glycine max*)	-	-	-
DDT and DDE	-	-	-
Some PCBs (See Organic Compounds that Affect the Skin)	-	-	-
Anti-androgenic Toxicants			
p,p'-DDT, and especially p,p'-DDE	-	-	-
Some PCBs (See Organic Compounds that Affect the Skin)	-	-	-
Estrogenic Compounds			
Endogenous estrogen-induced pancytopenia in the ferret	Ferrets	Any unmated female ferret	Months; very often lethal
Additional Toxicants			
Nonylphenol Plasticizer and component of some detergents and a surfactant used in pesticides; pollution may feminize aquatic animals, possibly terrestrial animals as well	-	-	-

Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation

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Annotated Table of Toxicants that Affect Peripheral Circulation and/or that May Cause Reduced Lactation

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
North American Poisonous Snakes (Rattlesnakes and other pit vipers)	All species	Minutes to hours	Several hours to days; potentially lethal
Brown Recluse Spider or Fiddle Back (*Loxosceles reclusa*) (*Loxosceles reclusa*) - Venom	All species	Minutes to hours	Days to months; rarely lethal; rarely recognized toxicosis
Ergot Alkaloids and Gangrenous Ergotism (Saint Anthony's Fire)	Cattle sheep	Days to weeks	Weeks; potentially lethal
***Festuca Arundinacea* - Tall Fescue** (*Festuca* infected with *Neotyphodium coenophianum*) (ergot alkaloid mycotoxin)	Cattle	Weeks to months	Weeks to months
***Juglans Nigra* - Black Walnut - Toxicosis in Horses**	Horses (cause of lamintis in horses)	12 - 24 hours	Days; rarely lethal unless 3rd phalanx rotates through the sole
***Berteroa Incana* - Hoary Alyssum**	Horses (leg swelling and lamintis)	1 - 2 days	Days to a week; rarely lethal
Thallium (See Toxicants that Affect the Skin)	All species	Hours to chronic	Days to permanent damage; often lethal

Hepatotoxic Chemicals and Drugs

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Annotated Table of Hepatotoxic Chemicals and Drugs

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Iron (Iron dextran and other iron compounds)	Dogs, piglets, other species	Minutes to chronic	Hours to permanent damage; acute death most common in piglets
Phosphorus	Dogs, other species	Hours to days	Days to permanent damage, often lethal
Carbon Tetrachloride	All species	Hours to days	Days to permanent damage; often lethal but toxicoses are rare
Phenolics and Coal Tar	All species	Hours to days	Days to permanent damage; often lethal
Nitrosamines	Sheep, human	Hours to chronic	Weeks to permanent damage, potentially lethal; toxicoses are rare
Thiacetarsemide Sodium (Caparsolate ®)	Dogs	One day to 3 weeks	Several days to weeks; often lethal
Mebendazole - (Telmin ®, Telmintic ®, Vermox ®) (idiosyncratic reaction)	Dogs	Around 2 weeks	Days to weeks; often lethal
Tannic Acid	All species	Hours to days	Days to weeks; potentially lethal
Copper (also: See Toxicants that Cause Hemolysis)	Sheep, cattle, certain breeds of dogs	Hours to Chronic	Days to permanent damage, often lethal
Dialkyltins (including metabolites of trialkyltins)	Wildlife	Chronic	Chronic
Acetaminophen	Dogs, cats	1 - 3 days	Days to permanent damage; often lethal
Formaldehyde	Dogs	Hours to days	Days to permanent damage; often lethal
Carbon disulfide (also: See Toxicants with Mixed Effects on the CNS)	All species	Hours to days	Days to permanent damage; often lethal
Halogenated hydrocarbons including halogenated dibenzodioxins (See Toxicants that Affect the Skin, Other Organic Compounds)	All species, especially top aquatic predators	Chronic	Weeks to permanent, potentially lethal
Pennyroyal oil (Used as insecticide)	See Organic Compounds that Affect the Lungs		

Mycotoxins that Affect the Liver

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Annotated Table of Mycotoxins that Affect the Liver			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Aflatoxins	Most Species	Days to Chronic	Weeks to permanent damage, potentially lethal
Sterigmatocystin	Most species	Weeks to chronic	Weeks to months; toxicoses very rare
Rubratoxins A and B	Chickens; possible cattle and swine	Days to chronic	Unknown; toxicoses rare
Sporodesmin	Cattle, esp. sheep	Chronic	Chronic reported primarily in Australia and New Zealand
Penicillic acid	Swine	Chronic	Chronic; toxicoses rare
Fumonisins (See Toxicants with Mixed Effects on the CNS)	Esp. horses	1 weeks to chronic	Weeks; often lethal in horses
Cyclopiazonic acid (rare)			

Poisonous Plants that Affect the Liver

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Annotated Table of Poisonous Plants that Affect the Liver

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Xanthium spp. - Cocklebur	Herbivores, swine	Hours to days	Days to permanent damage, often lethal
Senecio - Ragwort-Groundsel Pyrrolizidine alkaloid containing plant	Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal
Crotalaria - Rattlebox Pyrrolizidine alkaloid containing plants	Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal
Amsinckia - Fiddleneck Pyrrolizidine alkaloid containing plants	Herbivores, cattle, horses, pigs, poultry; sheep less susceptibleDays to weeks	Days to permanent damage; often lethal	
Echium spp. Pyrrolizidine alkaloid containing plants	Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal
Heliotropium (Heliotrope) Pyrrolizidine alkaloid containing plants	Herbivores, cattle, horses, pigs, poultry; sheep less susceptible	Days to weeks	Days to permanent damage; often lethal
Microcystis Aeruginosa, M. Viridis, Anabaena Flos-Aquae, Nostoc spp.,_Oscillatoria Aghardii_, and _Nodularia Spumigena_	All species	Hours (usually) to chronic	Days to permanent damage; highly lethal
Lantana and _Lippia_ spp.	Herbivores	Days to chronic	Weeks to permanent damage; often lethal
Helenium spp. - Sneezeweeds	Esp. sheep and goats, cattle, horses, swine, rabbits	Hours to chronic	Days to weeks; often lethal
Hymenoxys spp. - Rubberweed - Bitterweed	Esp. sheep and goats, cattle, horses, swine, rabbits	Hours to chronic	Days to weeks; often lethal
Kochia Scoparia	Ruminants	Hours to chronic	Days to weeks; potentially lethal
Lotus Corniculatus - Birdsfoot Trefoil	Ruminants; other herbivores	Chronic	Weeks to months; poisoning is rare
Cycad Poisoning _Cycas_ or _Zamia_ spp.	Herbivores, dogs, swine	Hours to a few days	Weeks to permanent damage; often lethal

Hepatogenous Photosensitizers

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Annotated Table of Hepatogenous Photosensitizers

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
***Tetradymia* - Artemisia Poisoning** Horsebrush (*Tetradymia glabatra* or *T. canescens*), especially when also grazing black sage (*Artemisia salina*)	Sheep	Hours to days	Days to weeks, potentially lethal
***Panicum* spp. - Panic Grasses** (Disogenin-containing plant)	Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal
***Tribulus* - Puncture Vine** (Disogenin-containing plant)	Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal
Nolina *Nolina texana* (Sacahuiste, bunchgrass) (Disogenin-containing plant)	Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal
***Agave Lecheguilla* - Agave** (Disogenin-containing plant)	Cattle, goats, and esp. sheep	Days to chronic	Days to months, potentially lethal
Blue-green algae (*microcystis*)	(See Poisonous Plants that Affect the Liver)		
Rape (*Brassica*)	(See Goitrogenic Plants)		
Kochia Scoparia	(See Poisonous Plants that Affect the Liver)		
Moldy post-frost Florida Bermuda Grass (Cynodon)	Herbivores	Days to weeks	Weeks to months
Pyrrolizidine alkaloids plants	(See Poisonous Plants that Affect the Liver)		
Lantana	(See Poisonous Plants that Affect the Liver)		
Sporodesmin (mycotoxin)	(See Mycotoxins that Affect the Liver)		

Note: Hereditary liver problem in Southdown sheep = a potential confusion factor

Section XI: Toxicants that Affect the Skin

Toxicants that Cause Skin Damage by Primary Photosensitization

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Annotated Table of Toxicants that Cause Skin Damage by Primary Photosensitization

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Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
***Hypericum* - St. Johnswort**	Herbivores	Within 24 hours to weeks	Days to weeks; rarely lethal
***Fagopyrum* - Buckwheat**	Herbivores	Within 24 hours to weeks	Days to weeks, rarely lethal
***Cymopterus* - Spring Parsley**	Sheep, cattle, birds	Within 24 hours to weeks	Days to weeks, rarely lethal
Phenothiazine (Thiodiphenylamine)	Calves, goats, sheep, fowl (horses are sensitive to penothiazine but apparently do not develop photosensitization)	Days	Days to weeks; potentially lethal

Toxicants that Cause Skin Effects other than Photosensitization

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Annotated Table of Toxicants that Cause Skin Effects other than Photosensitization

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
1. Metal that Affect the Skin			
Thallium	All species; esp. dogs	Hours to weeks	Weeks to months; very often lethal
Selenium	Most species	Chronic	Chronic; often lethal
Molybdenum Toxicosis - Copper Deficiency (Excess molybdenum/deficient copper in ruminants; see Toxicants that Cause Hemolysis)	Ruminants	Days to week	Days to chronic; often lethal
2. Other Organic Compounds that Affect the Skin			
Highly Chlorinated Naphthalenes	All species	Chronic	Chronic, potentially lethal, toxicoses rare in domestic species
Related Halogenated Aromatics	All species	Chronic	Chronic, often lethal, toxicoses rare in domestic species
Polychlorinated Biphenyls (PCBs)	All species	Chronic	Chronic; potentially lethal, toxicose rare in domestic species
Polybrominated Biphenyls (PBBs)	All species	Chronic	Chronic; potentially lethal, toxicose rare in domestic species
Turpentine	All species	Minutes	Hours to ddays; potentially lethal
Diesel Fuel (Petroleum hydrocarbons)	All species	Minutes to hours	Hours to days, rarely lethal
Kerosene (Petroleum hydrocarbons)	All species	Minutes to hours	Hours to days, rarely lethal
Other solvents	All species	Minutes to hours	Hours to days, rarely lethal
Formaldehyde and Formalin	All species	Minutes to hours	Hours to days, rarely lethal with skin only exposure, toxicoses rare
Phenolics	(See Toxicants that Affect the Liver)		
5-Fluorouracil (Effudex ®)	-	-	-
3. Other Plants that Affect the Skin (Integument)			
***Vicia villosa* - Hairy Vetch**	Herbivores	Chronic	Months; often lethal
***Hippomane Mancinella* - Manchineel Tree**	Most species	Minutes to hours	Days, rarely lethal

Section XII: Toxicants that Affect the Gastrointestinal Tract

Forms of Energy, Chemicals and Drugs that Affect the Digestive

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Annotated Table of Forms of Energy, Chemicals and Drugs that Affect the Digestive Tract

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Arsenic (Many sources, including ashes from CCA [wood-preservative]-treated lumber)	All species	Hours to chronic	1 - 7 days; often lethal
Antimony	All species	Hours to chronic	1 - 7 days; often lethal; toxicosis is rare
Chromates	All species	Hours to chronic	Days; potentially lethal
Fertilizer	All species	Up to 24 hours	1 - 3 days; rarely lethal in small animals; potentially lethal in ruminants
Molybdenum	Ruminants	Chronic	Days to weeks, potentially lethal
Elemental and Inorganic Salts of Mercury (acute)	See Toxicants with Mixed Effects on the CNS		
Lead (Acute)	See Toxicants with Mixed Effects on the CNS		
Thallium (Acute)	See Toxicants that Cause Skin Effects Other Than Photosensitization		
Cadmium (Acute)	See Toxicants that Affect the Kidneys		
Copper (Acute)	See Toxicants that Cause Hemolysis		
Phosphorus (Initial)	See Toxicants that Affect the Liver		
Zinc Phosphide (Initial)	See Toxicants Associated with Stimulation or Seizures		
Zinc (Acute)	See Toxicants that Affect the Kidneys		
Nonsteroidal Anti-Inflammatory Agents (See Toxicants that Affect the Kidneys)	Most species	Hours to days	Days to weeks; often lethal
Cardioglycosides	See Toxicants that Affect the Heart		
Fluroacetate (1080) (Acute) (Esp. Canids)	See Toxicants that Cause Seizures		
Cholinesterase Inhibitors	See Toxicants that Affect the Autonomic Nervous System		
Rotenone	See Toxicants With Mixed Effects on the CNS		
Carbon Tetrachloride	See Toxicants that Affect the Liver		
Chlorophenoxy Herbicides	See Toxicants that Affect Primary Muscle Dysfunction and/or Paralysis		
Blister Beetles (*Epicauta*)	See Toxicants that Affect the Kidneys		
5-fluorouracil (Effudex ®) Topical Creme (When Ingested)	See Toxicants Associated with Seizures		

ANTU	See Toxicants that Affect the Respiratory System		
Scombroid fishes (deteriorated tuna, bonito, mackerel) (histidine → histamine)	-	-	-
Dysautonomia Syndrome	-	-	-

Plants that Affect the Gastrointestinal Tract (Part I)

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Annotated Table of Plants that Affect the Gastrointestinal Tract (Part I)

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Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Proteins-Synthesis Inhibiting Lectins ("Toxalbulmins")			
***Abrus Precatorius* (Crab's Eye, Precatory Bean, Rosary Pea, Jequirity Bean)**	Horses, small animals	12 - 24 hours	Few days; often lethal
***Ricinus Communis* (Castor Bean, Castor-Oil-Plant, *Palma Christi*)**	Horses, dogs	12 - 36 hours	Few days; often lethal
Robinia	Horses, cattle	Hours	Days, potentially lethal
***Phoradendron* spp. and *Viscum* - Mistletoe**	Small animals	Hours	Days, potentially lethal
Irritant Oils			
***Ranunculus* spp. - Buttercups**	Herbivores	Hours	Days; infrequently lethal, poisoning is rare
***Caltha* - Marsh Marigold**	Herbivores	Hours	Days; infrequently lethal, poisoning is rare
Saponin - Contaning Plants			
***Phytolacca* - Pokeweed**	Herbivores	Hours to days	Days, potentially lethal
***Saponaria* spp.**	Herbivores	Hours to days	Days, potentially lethal
***Agrostemma Githago* - Corn Cockle**	Herbivores	Hours to days	Days, potentially lethal
***Hedera Helix* - English Ivy**	Most species	Hours to days	Days, potentially lethal
***Sesbania* spp.**	Herbivores, fowl	Hours to days	Days to week, potentially lethal
Purgative Glycosides			
***Helleborus Niger* - Christmas Rose**	Most species	Hours	Days, poisoning is rare

Trichothecenes

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Annotated Table of Trichothecenes

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Deoxynivalenol (vomitoxin)	Swine, cattle, dogs, and poultry	Hours to days	Days; unlikely to be lethal
T-2 toxin, HT-2 toxin, diacetoxysciprenol (DAS), related and macrocyclic trichothecenes	Cattle, swine, small animals, poultry	Hours to chronic	Days, potentially lethal

Other Mycotoxins, Bacterial Toxins, Zootoxins, and a Yet-To-Be Identified Agent that Affect the Gastrointestinal Tract

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Annotated Table of Other Mycotoxins, Bacterial Toxins, Zootoxins, and a Yet-To-Be Identified Agent that Affect the Gastrointestinal Tract

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Bacterial toxins (food poisoning; most garbage poisonings, most carrion toxicoses; bacteria-contaminated Christmas tree water)	Small animals	Minutes to hours	Days; very often lethal
Endotoxins and enterotoxins	All species	Minutes to hours	Days; often lethal
Staphylococcal enterotoxins	All species	Minutes to hours	Days; often lethal
Clostridial enterotoxins	Most species	Hours to days	Days; often lethal
Antibiotic-Induced Enterocolitis In the Horse, Guinea Pig, and Rabbit	Horses, rabbits, guinea pigs, other posterior fermenters	Hours to days	Days; very often lethal

Section XIII: Toxicants that May Affect the Oro-Pharyngeal and Gastrointestinal Tract

Chemical Agents Including Mycotoxins

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Annotated Table of Chemical Agents Including Mycotoxins

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Corrosive alkalis	All species	Seconds to hours	Hours to days; potentially lethal
Corrosive acids	All species	Seconds to hours	Hours to days; rarely lethal
Hypochlorites (concentrated forms)	Small animals	Seconds to hours	Days; rarely lethal
Formaldehyde	Dogs	Minutes to hours	Hours to days; often lethal
Phenolics (concentrated phenol or cresol)	(See Hepatotoxic Chemicals and Drugs)		
Cholinesterase inhibitors	(See Inhibitors of Cholinesterase)		
Moldly red clover (salframine)	(See Muscarinic Agonists)		
Trichothecene Mycotoxins	(See Toxicants that Affect the Gastrointestinal Tract)		

Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin

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Annotated Table of Miscellaneous Plants Causing Irritation of the Oral Cavity and the Skin

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Nettles (*Urtica* and *Laportea*) (contain histamine)	Most species	Minutes to hours	Days; rarely lethal *
Nettle spurge (*Cnidocolus*)	Most species	Minutes to hours	Days; rarely lethal *
Burdock (*Arctium lappa*)	Most species	Minutes to hours	Days; rarely lethal *
Wild Barley (*Hordeum*)	Most species	Minutes to hours	Days; rarely lethal *
Bromes (*Bromus*)	Most species	Minutes to hours	Days; rarely lethal *
Sandburs	Most species	Minutes to hours	Days; rarely lethal *
Goatheads (*Tribulus terrestris*)	Most species	Minutes to hours	Days; rarely lethal *
Numerous cacti	Most species	Minutes to hours	Days; rarely lethal *
* Potentially lethal with secondary infection, such as after perforation of a foreign body			

Plants of the Araceae Family (Plants Containing Oxalate Crystals and Histamine Releasers)

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Annotated Table of Plants of the Araceae Family (Plants Containing Oxalate Crystals and Histamine Releasers)

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Jack-in-the-pulpit (*Arisaema triphyllum*)	Most species	Minutes to hours	Days; potentially lethal; poisoning is rare
Dumbcane (*Dieffenbachia*)	Dogs, cats	Minutes to hours	Days; potentially lethal
Philodendron (*Philodendron* spp.)	Dogs, cats	Minutes to hours	Days; potentially lethal
Elephant's ear (*Colocasia* spp.)	Dogs, cats	Minutes to hours	Days; potentially lethal
Alocasia (*Alocasia* spp.)	Dogs, cats	Minutes to hours	Days; potentially lethal
Split-leaf philodendron (*Monstera deliciosa*)	Dogs, cats	Minutes to hours	Days; potentially lethal
Wild calla (*Calla*)	Most species	Minutes to hours	Days; potentially lethal
Skunk cabbage (*Symplocarpus*)	Most species	Minutes to hours	Days; potentially lethal
Arrowhead plant (*Syngonium*)	Most species	Minutes to hours	Days; potentially lethal
Others			

Section XIV: Toxicants that Affect the Heart

Cardioglycoside Toxicosis Including Red Squill and Scirriloside

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Annotated Table of Cardioglycoside Toxicosis Including Red Squill and Scirriloside

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
***Digitalis Purpurea* and Other Species of *Digitalis* - Foxglove**	Most species	Hours	Days; often lethal
***Nerium* - Oleander**	Most species	Hours	Days; often lethal
***Convallaria* - Lily of the Valley**	Most species	Hours	Days; potentially lethal
***Apocynum* - Dogbanes** Indian hemp	Most species	Hours	Days; potentially lethal
***Bufo* Toxicosis - Toad Poisoning**	Dog, cats	Minutes to hours	Days; often lethal
Red squill (rodenticide)	Dogs, cats	Minutes to days	Days; often lethal; not widely available
Scilliroside (rodenticide)	Dogs, cats	Minutes to hours	Days; often lethal; not widely available
Some milkweeds (*Asclepias*)	(See Toxicants Associated with CNS timulation or Seizures)		

Andromedotoxin (Grayanotoxin) - Containing Plants (Heath, Ericaceae Plant Family)

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Annotated Table of Andromedotoxin (Grayanotoxin) - Containing Plants (Heath, Ericaceae Plant Family)

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Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Rhododendron (Azalea and other strains of *Rhododendron*)	Esp. goats, most species	Hours	Several hours to days; often lethal
***Kalmia* - Laurels** Moutain laurel, common names include: - lambkill - sheepkill - calfkill	Esp. goats, most species	Hours	Several hours to days; often lethal
***Pieris* - Japanese Pieris**	Most species	Hours	Several hours to days, often lethal

Cardioglycoside-Like Plants

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Annotated Table of Cardioglycoside-Like Plants			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Aconitum **- Monkshood**	Most species	Hours	Days; often lethal
Mistletoe (*Phoradendron*)	(See Plants that Affect Gastrointestinal Tract)		

Other Plants that Affect the Heart

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Annotated Table of Other Plants that Affect the Heart			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
***Taxus* - Yew** (e.g., Japanese yew, Canada Yew, ground hemlock)	Most species	Hours	Days; often lethal
***Cassia* - Senna, Coffee Senna**	Cattle, fowl and other species	One day to chronic	Days to permanent damage; often lethal
***Zigadenus* - Death Camas**	Most species	Hours	Days (?), often lethal; poisoning is infrequent
Avocado (*Persea americana*) in cage birds	Caged birds, goats, other herbivores	12 hours to 2 days	Days; death usually occurs within 2 days of onset
White snakeroot (*Eupatorium rugosum*) (See Toxicants that Cause CNS Depression)	Horse	Days to chronic	Permanent damage
Jerusalem cherry (*Solanum pseudocapsicum*)	See Cholinergic Blockers		
Kleingrass (*Panicum*)	See Hepatogenous Photosensitizers		
False hellebore (*Veratrum californicum*)	(See Teratogens)		
Vitamin D-Containing Plants (*Solanum malacoxylon* and *Cestrum diurnum*)	(See Nephrotoxic Plants)		

Organic Compounds that Affect the Heart

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Annotated Table of Organic Compounds that Affect the Heart

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Monensin (Rumensin ®; Coban ®)	See Monensin section		
Lasalocid (Bovatec ®; Avatec ®)	See Lasalocid section		
Other ionophores	Most species	Hours to 2 days	Days to permanent damage; often lethal
Monensin	Most species	Hours to 2 days	Days to permanent damage; often lethal
Lasalocid	Most species	Hours to 2 days	Days to permanent damage; often lethal
Gossypol (constituent of cottonseed and cotton seed meal)	Swine, calves, horses, dogs, poultry	Weeks to a year	Weeks to permanent damage; often lethal
Urea and other non-protein nitrogen sources	(See Toxicants with Mixed Effects on the CNS)		
Xylazine	Most species	Minutes to hours	Hours; rarely lethal
Amitraz	(See Toxicants that Cause CNS Depression)		
Caffeine and other methylxanthines	(See Toxicants Associated with Central Nervous Stimulation or Seizures)		
Tricyclic Antidepressants	(See Toxicants with Mixed Effects on the Nervous System)		
Cocaine	(See Toxicants Associated with Stimulation or Seizures)		
Diphemanil methyl sulfate **(Diathal ®) and Anesthetics**	-	-	-
Blister Beetles	(See Toxicants that Affect the Kidneys)		
Cyclopiazonic acid (Mycotoxin) (rare)	-	-	-
Citreoviridin (Mycotoxin) (rare)	-	-	-
Moniliformin (Mycotoxin) (toxicoses may be rare, but furhter research seems to be warranted on potential occurence)	-	-	-
Batrachotoxin in poison dart frogs	-	-	-

Central and South America (*Dendrobates* and *Phyllobates*) (causes sodium channels to stay open without related changes in potassium or calcium. Also causes a massive release of acetylcholine in nerve-muscle preparations. Cause of death seems to be due to severe cardiac arrhythmias and cardiac arrest.)			

Section XV: Toxicants that Affect the Lungs

Inorganic Compounds that Affect the Lungs

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Annotated Table of Inorganic Compounds that Affect the Lungs

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Nitrogen Oxides (Silo Filler's Disease)	Most species	Minutes to hours	Hours to permanent damage, potentially lethal
Gaseous Ammonia	Most species	Minutes to chronic	Hours to permanent damage due to infection (usually upper respiratory), rarely lethal
Overheated Polytetrafluoroethylene - Teflon or Silverstone Overheated Teflon ® or Silverstone ® cookware (in birds)	Caged birds	Minutes to hours	Hours to permanent damage, highly lethal
High Doses of Selenium and Selenium Containing Plants (Acute)	See Metals and Metalloids that Affect the Skin		
Hydrochloric acid (HCl)	All species	Minutes to hours	Hours to 2 days, potentially lethal
Hydrofluoric acid (HF)	All species	Minutes to hours	Hours, poisoning very rare
Zinc phosphide (rodenticide) or aluminum phosphide (fumigant and general biocide)	See Toxicants Associated with CNS Stimulation or Seizures		

Organic Compounds that Affect the Lungs

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Annotated Table of Organic Compounds that Affect the Lungs

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Paraquat (A Dipyridyl Herbicide)	Most species	Hours to days	Days to permanent damage, often lethal
Alpha-Naphthyl Thiourea (ANTU)	Dogs, cats	6 - 12 hours	Days, highlty lethal
Crude Oil	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal
Kerosene	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal
Diesel fuel	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal
Gasoline and other light weight petroleum distillates (hydrocarbons)	All species	Hours to days	Days to permanent damage from aspiration pneumonia, potentially lethal
Ethylenediamine Dihydroiodide (EDDI)	Most species	Hours to chronic	Days, rarely lethal
Pennyroyal Oil - Ketone Pulegone	Cats, dogs	Hours	Hours to days, potentially lethal
Smoke Inhalation	All species	Minutes to hours	Hours to permanent damage, highly lethal
Organophosphorus or Carbamate Insecticides	See Inhibitors of Cholinesterase		
Freon (fluorocarbons, chlorofluorocarbons)	Small animals	Minutes to hours	Hours days, potentially lethal, poisonning is rare
Formaldehyde	All species	Minutes to chronic	Days, potentially lethal
Fumonisins	See Toxicants with Mixed Effects on the CNS		

Section XVI: Toxicants that Cause Asphyxia

Toxicants that Cause Asphyxia

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Annotated Table of Toxicants that Cause Asphyxia

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Carbon dioxide	All species	Minutes to hours	Minutes to hours; often lethal
Helium	All species	Minutes to hours	Hours; poisoning is rare
Hydrogen (also flammable)	All species	Minutes to hours	Hours; poisoning is rare
Aliphatic hydrocarbons (also explosive!; e.g. methane, ethane in natural gas)	All species	Minutes to hours	Hours; poisoning is rare
Nitrogen oxides	(See Inorganic Compounds that Affect the Lungs)		
Hydrogen sulfide	(See Toxicants that Cause Primarily Respiratory Paralysis)		

Section XVII: Toxicants that Inhibit the Function of Cytochromes

Toxicants that Inhibit the Function of Cytochromes

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Annotated Table of Toxicants that Inhibit the Function of Cytochromes

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Cyanide hydrogen cyanide = prussic acid, calcium cyanide, sodium cyanide, cyanide in some smokes	All species	Minutes to hours	Hours; extremely lethal
Wild black cherry (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Chokeberry (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Plum (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Peach (*Prunus*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Sudan grass and other *Sorghum* spp. [Cyanogenic glycoside-containing plant] (See Methemoglobin Producers)	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Arrowgrass (*Triglochin*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
White clover (*Trifolium*) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal (unlikely cause of toxicosis)
***Linum* spp. - Flax, Linseed** [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Some spurges (*Euphorbia*) (rare) [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Elderberry (leaves and stems) (*Sambucus*) [Cyanogenic glycoside-containing plant] (See Poisonous Plants that Affect the Gastrointestinal Tract)	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Rubberseed meal [Cyanogenic glycoside-containing plant]	All species, esp. herbivores	Minutes to hours	Hours; often lethal
Hydrogen sulfide	(See Toxicants that Primarily Cause Respiratory paralysis)		

Section XVIII: Toxicants that Decrease the Ability of Hemoglobin to Carry Oxygen

Carbon Monoxide

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Annotated Table of Carbon Monoxide			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Smoke Inhalation (Carbon monoxide gas from smoke and malfunctioning fossil fuel-burning heaters)	All species	Minutes to hours	Hours to 2 days, often lethal
Methylene Chloride (metabolized to carbon monoxide)	(See Toxicants that Cause CNS Depression)		

Methemoglobin Producers

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Annotated Table of Methemoglobin Producers

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Acetaminophen	Cats, dogs	4 - 24 hours	Days; highly lethal
Naphthalene (mothballs)	Dogs, cats	Hours	Days; often lethal
Local Anesthetics	Most species	Hours	Hours to a day; often lethal
Resorcinol in cats	Mostly cats	Hours	Days; often lethal
Nitrate and nitrite	Ruminants, occasionally other species	Minutes to hours	Hours to 2 days; often lethal
Nitrate-accumulating plants, e.g.:	Ruminants, occasionally other species	Hours to days	Hours to 2 days; often lethal
Sorghum (*Sorghum*), Sudan grass	(See Cyanogenic Glycoside-Containing Plants)		
Corn, especially green chop (*Zea mays*)			
Oats (*Avena sativa*)			
Wheat (*Triticale*)	-		
Beets (*Beta*)	(See Toxicants that Affect the Kidneys)		
Kochia	(See Poisonous Plants that Affect the Liver)		
Locoweeds (organic nitrates)	(See Toxicants with Mixed Effects on the CNS)		
Fiddleneck (*Amsinckia*)	(See Poisonous Plants that Affect the Liver)		
Fescue (*Festuca*)	(See Toxicants that Affect Peripheral Circulation) (Methemoglobinemia is rare)		
Pigweed (*Amaranthus*)	(See Plants that Affect the Kidneys) (Methemoglobinemia is rare)		
Lamb's quarters (*Chenopodium*)	(See Plants that Affect the Gastrointestinal Tract) (Toxicosis is rare)		
Many others	-		
Chlorates	All species	Hours	Hours to days

Section XIX: Toxicants that Cause Hemolysis

Toxicants that Cause Hemolysis

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Annotated Table of Toxicants that Cause Hemolysis

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Red Maple (*Acer Rubrum*) Poisoning	Horses	1 - 6 days	Days; often lethal
Onion (*Allium*) Poisoning (onion and garlic)	Dogs, cattle, other species	Hours to days	Days; potentially lethal
Copper	Sheep, cattle, certain breeds of dogs	Hours to chronic	Days; often lethal
Arsine (arsenic hydride) gas which may come from charging storage batteries	All species	Minutes to hours	Days often lethal; poisoning is rare
Stibine (antimony hydride) gas	All species	Minutes to hours	Days often lethal; poisoning is rare
Phenothiazine	(See Toxicants that Cause Primary Photosensitization)		
Propylene glycol (especially when given IV)	All species	Hours	Days potentially lethal; particularly after a high intravenous dose
Rattlesnakes and other pit vipers (phospholipase A)	All species	Minutes to hours	Days potentially lethal
Saponin-containing plants	(Hemolysis is theoretically possible, but not well documented, see Poisonous Plants that Affect Gastrointestinal Tract)		
***Brassica* spp.** (kale, brussels sprouts, rapeseed and forage)	(See Toxicants that Cause Goiter)		
Zinc	(See Toxicants that Affect the Kidneys)		

Section XX: Coagulation of Blood and the Function of Vitamin K

Toxicants that Interfere with the Function of Vitamin K

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Annotated Table of Toxicants that Interfere with the Function of Vitamin K

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Toxicants that Interfere with the Function of Vitamin K			
Damaged or Moldy Sweet Clover Hay (*Melilotus*)	Cattle	Weeks to months	Days to weeks; often lethal
Moldy *Lespedeza* Hay	Ruminants	Weeks to months	Days to weeks; often lethal
Coumarin and indandione anticoagulant rodenticides and pharmaceuticals	Most species	2 days to a week	Days to 6 weeks; often lethal
Idiopathic Coagulopathy in Swine	Swine	No etiologic agent known	Days to weeks; often lethal
Toxicants that Affect the Liver and Secondarily Cause a Coagulopathy			
Aflatoxin and many other hepatotoxic agents	See Mycotoxins that Affect the Liver		
Many others			
Toxicants that Harm the Bone Marrow			
Bracken fern Pteridium	See Thiaminase-Containing Plants and Other Substances		
Trichloroethylene-extracted soybean oil meal	-		
Benzene	-		
Lead	See Toxicants with Mixed Effects on the CNS		
Cadmium	See Toxicants that Affect the Kidneys		
Chloramphenicol	-		
Toxicants that may Cause Severe Shock and Either Disseminated Intravascular Coagulation or Other Coagulopathy			
Synthetic and natural estrogens	-		
Lindane in human beings	-		
Garbage Toxicoses	See Toxicants that Cause Shock		
Pit Vipers	See Toxicants that Cause Shock		

Toxicants that Interfere with the Function of Vitamin K

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Annotated Table of Toxicants that Interfere with the Function of Vitamin K			
Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Toxicants that Interfere with the Function of Vitamin K			
Damaged or Moldy Sweet Clover Hay (*Melilotus*)	Cattle	Weeks to months	Days to weeks; often lethal
Moldy *Lespedeza* Hay	Ruminants	Weeks to months	Days to weeks; often lethal
Coumarin and indandione anticoagulant rodenticides and pharmaceuticals	Most species	2 days to a week	Days to 6 weeks; often lethal
Idiopathic Coagulopathy in Swine	Swine	No etiologic agent known	Days to weeks; often lethal
Toxicants that Affect the Liver and Secondarily Cause a Coagulopathy			
Aflatoxin and many other hepatotoxic agents	See Mycotoxins that Affect the Liver		
Many others			
Toxicants that Harm the Bone Marrow			
Bracken fern Pteridium	See Thiaminase-Containing Plants and Other Substances		
Trichloroethylene-extracted soybean oil meal	-		
Benzene	-		
Lead	See Toxicants with Mixed Effects on the CNS		
Cadmium	See Toxicants that Affect the Kidneys		
Chloramphenicol	-		
Toxicants that may Cause Severe Shock and Either Disseminated Intravascular Coagulation or Other Coagulopathy			
Synthetic and natural estrogens	-		
Lindane in human beings	-		
Garbage Toxicoses	See Toxicants that Cause Shock		
Pit Vipers	See Toxicants that Cause Shock		

Section XXI: Toxicants that Affect the Teeth and Skeletal System

Toxicants that Affect the Teeth and Skeletal System

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Annotated Table of Toxicants that Affect the Teeth and Skeletal System

Specific Agents	Major Species	Usual Time of Onset	Usual Duration (if survives)
Acute and Chronic - Fluoride Toxicosis (Fluorosis)	All species	Chronic	Essentially permanent; potentially lethal
Tetracyclines	Esp. young animals	Chronic	Essentially permanent; unlikely to be lethal
Congenital porphyria (confusion factor)	-		
Enrofloxacin	Young animals	Days to weeks	Essentially permanent; rarely lethal
Thiram (fungicide)	Poultry (chickens)	Chronic	Permanent (shortened bones); unlikely to be lethal
Vitamin A	Cats	Chronic	Essentially permanent (cervical spondylosis); potentially lethal
Cadmium	See Toxicants that Affect the Kidneys		
Molybdnenum **toxicoses / copper deficiency**	See Toxicants that Cause Skin Effects Other than Photosensitization		
Iron	See Toxicants that Affect the Liver		
Cyclopiazonic acid (rare)	-		

Toxicants that Cause Blindness

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Annotated Table of Toxicants that Cause Blindness

Specific Agents	
Ivermectin	(See Toxicants that Cause Central Nervous System Depression)
Ammonia (Corneal Damage) in Poultry	(See Inorganic Compounds that Affect the Lungs)
Phenylarsonics	(See Toxicants that Cause Paralysis)
Lead	(See Toxicants with Mixed Effects on the Central Nervous System)
Hexachlorophene	(See Toxicants with Mixed Effects on the Central Nervous System)
Bromethalin	(See Toxicants with Mixed Effects on the Central Nervous System)
Carbon disulfide	(See Toxicants with Mixed Effects on the Central Nervous System)
Methanol in Primates	(See Toxicants that Cause Acidosis)
Water Deprivation/Sodium Ion Toxicosis	(See Toxicants Associated with Central Nervous System Stimulation or Seizures)
Vitamin A (Deficiency or Chronic Toxicosis)	-
Rapeseed (*Brassica*)	(See Toxicants that Cause Goiter)
Cocklebur (*Xanthium*)	(See Poisonous Plants that Affect the Liver)
Buttercup (*Ranunculus*)	(See Plants that Affect the Digestive Tract, Irritant Oils)
Manchineel tree (*Hippomane*)	(See Other Plants that Affect the Skin)
Desert spike (*Oligomeris*)	(See Toxicants that Cause Stimulation or Seizures)
Phenothiazine-Induced Corneal Damage	(See Toxicants that Affect the Skin (Photosensitization))
Other Photosensitizers	(See Hepatogenous Photosensitizers and Toxicants that Cause Skin Damage by Primary Photosensitization; includes *Ammi majus* or *Cymopterus watsonii* fed to poultry - pigmentary retinopathy)
Vacor ® (Pyriminil; banned rodenticide)	(See Toxicants with Mixed Effects on the Central Nervous System)

Toxicants that Cause Bloat in Ruminants

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Annotated Table of Toxicants that Cause Bloat in Ruminants

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Alfalfa (*Medicago sativa*)	Ruminants	Hours	Hours to a day; often lethal
Soybean overload (*Glycine max*)	Ruminants	Hours	Hours to a day; may be lethal
Diet changes	Ruminants	Hours to 2 days	Days; often lethal
Sweet crude oil (Hydrocarbons)	(See Toxicants that Affect the Respiratory System)		
Ammonia toxicoses (urea)	(See Toxicants with Mixed Effects on the CNS)		
Bacteria that form insoluble slime	[See Bartley et al. Digestion and Metabolism in the Ruminant. (1975) pp.551-562.]		

Toxicants that Cause Shock

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Annotated Table of Toxicants that Cause Shock

Specific Agents	**Major Species**	**Usual Time of Onset**	**Usual Duration (if survives)**
Rumen overload	Ruminants	Hours	Days to weeks; often lethal
Garbage	(See Other Mycotoxins, Bacterial Toxins and Zootoxins that Affect the Gastrointestinal Tract)		
Arsenic	(See Toxicants that Affect the Gastrointestinal Tract)		
Some snake bites	(See Toxicants that Affect Peripheral Circulation)		
Iron dextran	(See Toxicants that Affect the Liver)		
Sulfonamides	(See Toxicants that Affect the Kidneys; see also Histamine)		
Polysorbate 80 in dogs (Tween 80®) (Histamine releaser) (drug vehicle)	-		
Numerous biologicals (Anaphylaxis)	-		
Other drugs	-		